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## **MRI-guided or assisted interventions for congenital heart disease**

Tzifa, Aphrodite

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# **MRI-guided or assisted interventions for congenital heart disease**

**Dr Aphrodite Tzifa, FRCPCH**

King's College London

A thesis submitted for the degree of Doctor of Medicine in Research

# ABSTRACT

---

Congenital heart disease occurs in 0.8-1% of children. A proportion of these patients will require interventional treatment in the form of cardiac catheterisation or surgery, whilst some will only require medical therapy. Echocardiography is the investigation of choice for diagnosis and follow-up of these patients, whilst magnetic resonance imaging (MRI) is now increasingly used in most centres to assess complex congenital cases and to answer specific questions, not possible to address with echocardiography. The ability to obtain anatomical together with quantitative physiological information, such as cardiac function and flows in one examination has led to more detailed assessment and analysis of congenital heart defects and continues to improve our understanding about congenital heart disease and its treatment options.

Cardiac MRI scans have now mostly replaced cardiac catheterisation procedures, routinely performed up to a few years ago to aid diagnosis. In parallel, a new form of hybrid catheterisation has emerged by combining MRI with simultaneous pressure measurement in different cardiac chambers and vascular structures. The combination of X-Ray and MRI guided (XMR) catheterisations can address clinical questions, such as estimation of pulmonary vascular resistance and cardiac output response to stress accurately, without the limitation of haemodynamic assumptions during calculations. Further to more accurate physiological information, XMR catheterisation can also offer detailed anatomical information of structures not well seen on echocardiography or MRI alone, and most importantly limit or eliminate the radiation exposure to patient that have been repetitively exposed to X-Ray radiation.

The purpose of the research work presented was two-fold: a. to extend the potentials of XMR-guided cardiac catheterisations, particularly in the area of pre-operative and post-interventional evaluation of congenital heart disease and b. to advance our already established programme of solely MR-guided *diagnostic* cardiac catheterisations in order to materialise the first-in-man solely MR-guided *therapeutic cardiac* catheterisations. In this way, transcatheter interventional procedures were aimed to be performed in the MR scanner in a similar fashion and with similar equipment to the ones used in the traditional catheterisation suite, without the exposure to ionising radiation. The work towards materialisation of this idea and the world-first clinical trial on solely MRI-guided cardiac interventions for congenital heart disease are being presented in this thesis.

## **STATEMENT OF ORIGINALITY**

---

I declare that the research work in this thesis has been primarily carried out by me. There are sections where other investigators have contributed towards the materialisation of this research work and these are outlined below:

The research work on the manufacturing, testing and optimisation of the MRI safe and compatible guidewire prior to the pre-clinical trial was carried out by Philips Research Laboratories, Eindhoven, The Netherlands (Sascha Krueger, Stephen Weiss), Hemoteq AG, Wuerselen, Germany (Matthias Von Walter, Marita Linssen) and the Fraunhofer Institute for Applied Information Technology, Aachen, Germany (Adrian Schuette). The sterilisation and preparation of the guidewire for the clinical trial was performed by Contract Medical International.

In addition I declare that this thesis has not been submitted elsewhere for a higher degree. I carefully explained the studies to the parents and patients with congenital heart disease and obtained their written consent where appropriate. I organised for the studies to be undertaken at the Evelina Children's Hospital, St Thomas' Hospital. I drafted and submitted the study proposals and obtained approval for the first-in-man interventional cardiac catheterisation clinical trial by the King's Hospital Ethics Committee, the Research and Development Department of Guy's and St Thomas' Hospital and the UK Medicines and Healthcare Products Regulatory Authority. I personally consulted all the quoted references.

Dr Aphrodite Tzifa, FRCPCH

## ACKNOWLEDGEMENTS

---

I would like to acknowledge the guidance, support and enthusiasm of my supervisors; Professor Reza Razavi and Professor Shakeel Qureshi. I am very grateful to Shak Qureshi who has taught me how to treat children and adults with congenital heart disease by performing percutaneous cardiovascular interventions and to Reza Razavi who opened my horizons and advanced my training by steering me into MRI. Professors Qureshi and Razavi have conveyed high mindedness, right ambition, wittiness and modesty within the virtuous mean taught by Aristotle's writings in the Academy of Athens. I would like to quote for them from my heart the words that Alexander the Great said about his tutor Aristoteles: 'Εἰς τοὺς γονεῖς μου ὀφείλω τὸ ζεῖν εἰς δὲ τοὺς διδασκάλους μου τὸ εὖ ζεῖν' [...To my parents I owe my being and to my teachers my well being...]

My years of research in the interventional MRI field were a unique experience and this was enhanced by the friendship and support of my colleagues within the Rayne Institute and the Department of Paediatric Cardiology at the Evelina Children's Hospital, who have been to me my extended family.

I thank the scientists at the Fraunhofer Institute, Hemoteq AG and Philips Research Laboratories, who played a definitive role in the materialisation of the first-in-man MR-guided cardiac interventions.

Finally, I would like to thank all of the parents of children and the adult patients with congenital heart disease who took part in this research, the nursing and Consultant staff at the Evelina Children's Hospital and my husband Constantinos Anagnostopoulos who has been an enormous source of confidence and inspiration in executing and finishing this work.

*To my husband Dinos  
and darling daughter Julia*

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## ABBREVIATIONS

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MRI: Magnetic resonance Imaging  
i-MRI: Interventional MRI  
XMR: Hybrid X-Ray and MRI guidance  
CHD: Congenital heart disease  
PVR: Pulmonary vascular resistance  
PVRI: Pulmonary vascular resistance index  
IVC: Inferior vena cava  
SVC: Superior vena cava  
RA: Right atrium  
LA: Left atrium  
RV: Right ventricle  
PA: Pulmonary artery  
RVOT: Right ventricular outflow tract  
LVOT: Left ventricular outflow tract  
RPA: Right pulmonary artery  
RPA-TP: Right pulmonary artery – through plane  
LPA: Left pulmonary artery  
LPA-TP: Left pulmonary artery – through plane  
PA-TP: Main pulmonary artery – through plane  
Ao: Aorta  
Ao-TP: Aorta- through plane  
SA: Short axis view  
R2CH: R2 chamber  
SSFP: Steady State Free Precession  
FA: Femoral artery  
AS: Alagille syndrome  
BA: Biliary atresia  
LT: Liver transplantation  
ACT: Activated clotting time  
ASTM: American Society for Testing and Materials  
SAR: Specific absorption rate  
RF: Radiofrequency



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1. MR-imaging guided cardiovascular interventions in young children.  
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3. Cardiovascular MR dobutamine stress in adult tetralogy of Fallot: disparity between CMR volumetry and flow for cardiovascular function.  
Valverde I, Parish V, **Tzifa A**, Head C, Sarikouch S, Greil G, Schaeffter T, Razavi R, Beerbaum P. *J Magn Reson Imaging*. 2011 ;33:1341-50
4. MR-Guided Cardiac Interventions Using MR-Safe Passive Devices: A Preclinical Study And First- In -Man Congenital Interventions  
**Tzifa A**, Krombach GA, Krämer N, Krüger S, Schütte A, von Walter M, Schaeffter T, Qureshi S, Krasemann T, Rosenthal E, Schwartz CA, Varma G, Buhl A, Kohlmeier A, Bucker A, Günther RW, Razavi R. *Circulation Cardiovasc Interv*. 2010 Nov 23

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**Tzifa A**, Pushparajah K, Bell AJ, Valverde I, Wong J, Charisopoulou D, Greil G, Beerbaum P, Bellsham-Revell HR, Hussain T, Rosenthal E, Krasemann T, Miller O, Qureshi SA, Razavi R. Card Young 2013: Supplement. AEPC abstract
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Hussain T; Peel S; **Tzifa A**; Krasemann T; Greil G; Botnar R. JCMR 2011;13:p23

# CHAPTER 1. SUMMARY

---

## 1.1. Introduction

Congenital heart disease occurs in 0.8-1% of children. A proportion of these patients will require interventional treatment in the form of cardiac catheterisation or surgery, whilst some will only require medical therapy. Echocardiography is the investigation of choice for diagnosis and follow-up of these patients, whilst magnetic resonance imaging (MRI) is now increasingly used in most centres to assess complex congenital cases and to answer specific questions, not possible to address with echocardiography. Diagnostic cardiac catheterisation is another important tool performed prior to planning palliative or corrective surgical procedures. During a cardiac catheterisation procedure, the cardiac anatomy is defined with the aid of ventriculograms and angiograms performed with contrast agents and under X-Ray fluoroscopic guidance. In addition, haemodynamic assessment as well as assessment of the physiology (shunts, Qp:Qs etc) can be performed.

In most recent years cardiac MRI scans have replaced diagnostic cardiac catheterisation procedures to a significant degree, by providing the anatomic as well as the above mentioned physiological details with great accuracy. To this end, cardiac catheterisations nowadays are mostly reserved for cases where haemodynamic assessment is essential or when the performance of a percutaneous intervention is anticipated. In parallel, a new form of hybrid catheterisation has emerged by combining MRI with simultaneous pressure measurement in various cardiac chambers and vascular structures. Paired X-Ray and MRI guided (XMR) catheterisations can address clinical questions, such as estimation of pulmonary vascular resistance and cardiac output response to stress accurately, without the limitation of haemodynamic assumptions made during calculations. Further to more accurate physiological information, XMR catheterisation can also offer detailed anatomical information of structures not well seen on echocardiography or MRI alone, such as small aortopulmonary collateral arteries, so that fluoroscopy and MRI can be combined in one procedure to avoid two general anaesthetic sessions in the same child and for the same purpose. Most importantly, hybrid XMR guided catheterisations can reduce significantly the patient radiation exposure. This is very important in this particular patient population due to the specific risks and concerns

raised with regards to the cumulative exposure risk to patients who need repetitive assessments and treatments involving ionising radiation.

To this end, beyond the replacement of diagnostic cardiac catheterisations by more sophisticated echocardiographic studies and magnetic resonance scans, back in 2002 our group pioneered the first-in-man sole MRI guided diagnostic cardiac catheterisation procedures for patients where haemodynamic assessment of their congenital cardiac defect was essential. A further goal since has been a. to extend the potentials of XMR-guided cardiac catheterisations, particularly in the area of pre- and post-operative and interventional evaluation of congenital heart disease and address physiological questions (such as response of cardiac output and haemodynamic measurements during pharmacological stress) b. to advance our already established programme of solely MR-guided *diagnostic* cardiac catheterisations in order to materialise the first-in-man solely MR-guided *therapeutic* cardiac catheterisations. In this way, transcatheter interventional procedures were aimed to be performed in the MR scanner in a similar fashion and with similar equipment to the ones used in the traditional catheterisation suite, without the exposure to ionising radiation.

## **1.2. Methodology**

The XMR interventional suite at the Evelina Children's Hospital was used to continue with an advanced XMR catheterisation programme and also perform MRI-guided cardiac catheterisations. The XMR suite was equipped with all the necessary monitors and essential equipment and was configured like a conventional cardiac catheterisation laboratory. In particular, the suite was equipped with an angiographic pump and the invasive pressure monitoring was connected to the in-room consoles placed directly in front of the MRI scanner. Multiple projectors were set up to display real-time magnetic resonance imaging, scanner control and the same haemodynamic recording system as in the traditional catheterisation laboratory (Figures 1-1 and 1-2). By configuring the XMR laboratory like a traditional cardiac catheterisation laboratory, cardiac catheterisations could be undertaken in the MRI-suite with safety, whilst X-Ray back-up was present in case of an urgent need to switch to the X-Ray modality.

In parallel, in vivo testing of a new MRI-compatible and safe guidewire manufactured in Germany took place in 2 animals (swine). The initial remarks and problems identified, mainly with its hydrophilic coating, led to the in vitro improvement of the guidewire and a

further trial to perform solely MR-guided interventions using this guidewire in 4 more swine was performed. The new pre-clinical in vivo testing proved the guidewire to be successful in aiding sole MRI-guided interventions, such as ballooning the pulmonary artery branches, the aorta and the aortic and pulmonary valves. Following the successful pre-clinical animal study, approval was obtained by a specialist device Ethics committee and the UK Medicines and Healthcare Regulatory Authority to commence the first-in-man clinical trial of MRI-guided percutaneous interventions for congenital heart disease.

The work towards materialisation of this idea and the world-first clinical trial on solely MRI-guided cardiac interventions are being presented in detail in this thesis.

### **1.3. Results**

The first-in-man sole MRI-guided interventional programme was commenced with the performance of 7 MRI-guided interventions in both children and adults with congenital heart disease. In particular, seven patients aged 3 - 64 years were included in the trial. Five patients underwent successful interventions for pulmonary valve stenosis (n=4) and native aortic coarctation (n=1). One patient with left pulmonary artery stent underwent right heart catheterisation with the aid of the new MR-wire, but due to low gradient across the stent no intervention was required. The last patient (8 year old child) with severe aortic stenosis had an unsuccessful attempt at ballooning the aortic valve, due to the inability of turning the wedge catheter into the ascending aorta, as the balloon of the catheter kept being pushed back by the aortic stenosis jet. This patient was then referred for X-Ray guided balloon dilation of the aortic valve.

Catheter manipulations were monitored with real time MRI sequence with interactive modification of imaging plane and slice position. Temporal resolution was 11-12 frames/sec. Median procedure and catheterisation times were 180 and 110 min, respectively. All patients who underwent successful MRI-guided interventions, except for the last, were discharged home the day after the procedure with > 50% reduction of the stenosis gradient and no procedural complications.

Beyond the world-first clinical trial on MRI-guided interventions, the XMR programme was advanced to include patients with complex haemodynamics or unknown cardiac output response to stress, such as in the case of pre-liver transplantation children. By equipping the XMR suite with an angiographic pump and all the necessary equipment found in a traditional

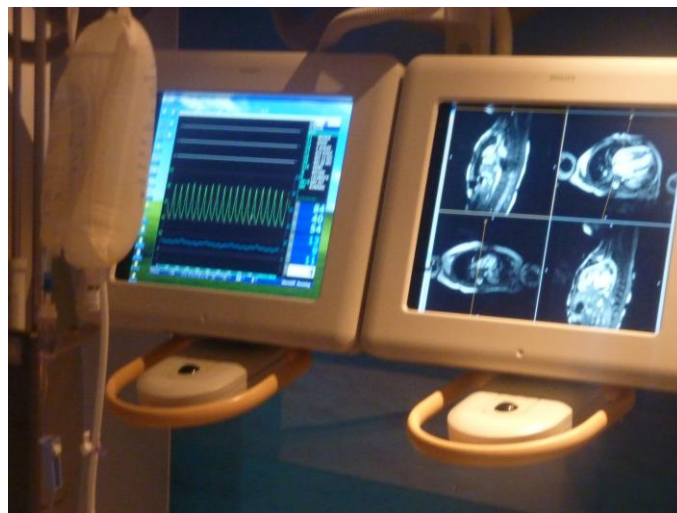
cardiac catheterisation lab, patients requiring anatomical assessment for complex anatomy (such as Fallot with pulmonary atresia and major aortopulmonary collateral arteries), not well imaged with echocardiography or MRI, became possible to evaluate by combining an MRI study and a diagnostic cardiac catheterisation / angiogram in one procedure. In addition, sole MRI-guided diagnostic cardiac catheterisations were advanced further to include the potential for test occlusion of Fontan fenestrations and intracardiac shunts.

## **1.4. Discussion**

Interventional MRI has been used in the past decade with the main aim to improve image guidance and limit the radiation exposure to patients and medics alike. It is thought that the beneficial effects of limiting the radiation exposure will be particularly important in children and adults with congenital heart disease. These patients are subjected to several procedures involving radiation in their lifetime such as X-Ray radiograms, cardiac catheterisations, CT scans etc. Being able to limit the radiation exposure is crucial, especially in the younger and immature patients. To this end, after a successful MRI-guided diagnostic cardiac catheterisation programme, we sought to expand and successfully performed the first-in-man sole MRI-guided percutaneous interventions. In addition, where sole MRI guidance was not possible, complex hybrid XMR catheterisations were performed to aid diagnosis and management, whilst limiting radiation exposure to a minimum. An increasing number of medical centers are now using hybrid XMR catheterisations, not necessarily performed in the same suite but also in adjacent labs. New MRI-compatible and safe equipment are being manufactured and tested and novel MRI sequences are being developed to assist in the performance of real-time interventional MRI. Although interventional MRI is still a research tool, it is envisaged that with the current advances taking place, sole MRI-guided interventions will become more routine in the future, at least for patients where precise 2D and 3D anatomy may be helpful for the performance of a percutaneous intervention.



**Figure 1-1.** The XMR interventional suites at the Evelina Children's Hospital, St Thomas' Campus (top) and Guy's Hospital, Guy's campus (bottom)



**Figure 1-2.**

The in-room monitors display real-time MRI images and haemodynamic pressure traces during the MR-guided intervention. They can be moved across both the bottom end and the top end of the magnet to be in proximity to the interventional Cardiologist.

## **CHAPTER 2. INTRODUCTION**

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### **2.1. Description and Epidemiology of Congenital heart disease**

Congenital heart disease is the commonest single group of congenital anomalies, accounting for about 30% of their total. Malformations of the heart occur during embryogenesis and they result from developmental errors during cardiac development. The cardiac malformations follow specific patterns, just as other malformations do, and these patterns present variability in their gradation. There are 8 common congenital heart disease lesions that account for about 80% of all cases (ventricular and atrial septal defect, patent ductus arteriosus, tetralogy of Fallot, pulmonary stenosis, coarctation of the aorta, aortic stenosis and transposition of the great arteries). The remaining 20% of congenital heart lesions represent more rare and complex lesions.

The collective incidence of congenital heart disease is 0.8% of live births. In 0.4% of live births the disease is moderate and may not need treatment, whilst in the other 0.4% the disease may need medical, transcatheter or surgical treatment. With the advancement of the therapeutic options available, approximately 85% of infants born with congenital heart disease in developed countries reach adulthood.

### **2.2. Increased survival and complications**

The first congenital cardiac operation performed was in 1938 by Robert Gross who ligated a patent ductus arteriosus in a 7 year old child. A few years later, in 1944, the end of a subclavian artery was anastomosed to a pulmonary artery in a patient with Tetralogy of Fallot to create a Blalock-Taussig shunt. Corrective heart surgery of more difficult and complex lesions started taking place in the 60's and 70's. Nowadays, the operative mortality of complex lesions can be as low as 1-3%. As a result, there is a growing population of patients that reach adulthood. It is estimated that in the United States there are more adults with congenital heart disease than there are infants and children and approximately 20.000



operations are performed annually in this patient population. Understanding the pathophysiology of their disease and the progression or alterations of their haemodynamics is vital in order to guide their management, medical or interventional. To this end, detailed assessment made by modern echocardiographic techniques, cardiac catheterisation and MRI are combined to provide as much data as possible for clinical and research purposes. Improved understanding and better management of patients with congenital heart disease from the onset of the disease detection is expected to lead to better long term outcomes.

### **2.3. Imaging congenital heart disease**

A few decades ago, a chest radiograph and thorough clinical examination used to be all that was available to categorise the patient's congenital heart disease and make a broad diagnosis. With the emergence of echocardiography, the diagnosis of congenital heart disease became precise and accurate. Echocardiography provides 2-dimensional and colour Doppler assessment, but also 3D anatomical detail, particularly good for the atrioventricular valve anatomy. In addition, tissue Doppler and speckle tracking that have been more broadly applied recently, can help in assessing the patient's cardiac function in more detail. Volumetric assessment using 3D echocardiography can be used for assessment of left ventricular volumes, but less well for the right ventricle, due to the proximity of the latter to the chest wall.

Cardiac magnetic resonance imaging (CMR) emerged more than a decade ago and initially found broad acceptance in supplementing the diagnosis making, by providing imaging of complex lesions together with 3D imaging of the cardiac structures. Since then, CMR has developed to a degree that nearly every complex patient undergoes a cardiac MRI scan prior to a planned intervention, in order to obtain information relating to the patient's physiology and exact anatomy.

MRI is particularly useful for accurate assessment of Qp:Qs and other shunts through cardiac chambers, vessels or prosthetic grafts. It can identify anatomical stenosis, even of small vessels, eliminating the need for cardiac catheterisation and provides ventricular function and volumetries with great accuracy. Although these days there are set protocols for examining different congenital heart disease entities, most of the sequences used are the same and interchange within the protocols to target the anatomy in question. The most frequent

sequences used during a CMR examination for assessment of congenital heart disease are discussed below.

## **2.4. Imaging congenital heart disease with cardiac magnetic resonance imaging**

### **2.4.1. Physical principles of magnetic resonance imaging**

Magnetic resonance is a phenomenon that arises when nuclei with a characteristic spin quantum number that is greater than zero are placed in a magnetic field. The spin characteristic of the charged nucleus induces a magnetic field with a magnitude and direction represented by the magnetic moment ( $\mu$ ). In the absence of an external magnetic field, the magnetic moments in a collection of nuclei will be randomly orientated. However, when a static magnetic field is applied, these magnetic moments assume discrete orientations, either parallel or anti-parallel to the direction of the applied field. In the absence of thermal fluctuations, nuclei will eventually obtain parallel orientation with the imposed field because this is the lowest energy state. The surfeit of nuclei that are parallel over those that are anti-parallel is called polarisation and results in a net macroscopic nuclear magnetisation. This is a small effect with a polarisation of only about 1 in  $10^5$  for hydrogen nuclei in a 1 Tesla field. For this reason large polarising magnetic fields are required. For clinical imaging, 0.5 to 3 Tesla field strengths are currently used.

If the nuclear polarisation is perturbed so that it is no longer aligned with the static polarising field, it rotates around the direction of the imposed magnetic field. This motion is called precession. The rate of precession is dependent upon the characteristics of the nuclear species and the strength of the field. Because the precession frequency depends on the magnetic field strength, and the MRI process requires the coordinated response of many nuclei to produce a detectable signal, the polarising field must be highly uniform.

RF energy is absorbed from the transmitter coil, this causes the polarisation, or net magnetic vector (NMV), to rotate from its equilibrium direction parallel to the static magnetic field through an angle which depends on the strength and duration of the RF pulse. If a  $90^\circ$  pulse is applied the NMV is rotated from the longitudinal direction to the transverse plane. The transverse component of the NMV induces an electromotive force (EMF) in a receive coil, which produces a measurable signal that can then be recorded and stored for further analysis.

#### **2.4.1.1. Relaxation**

Following the application of the RF pulse, the NMV returns to equilibrium and re-aligns with the main magnetic field, through a relaxation processes. Relaxation is influenced by the environment in which the spins exist, and is the basis of image contrast in conventional MRI.

There are two distinct relaxation processes, which occur with exponential time courses. T1 recovery, or spin–lattice relaxation, depends on the energy transfer between spins and the surrounding lattice. T1 recovery is the process by which longitudinal magnetisation is restored after an RF pulse. The value of T1 in biological tissue ranges from about 50 milliseconds (ms) to a few seconds, depending on the kind of nuclei being stimulated, their chemical and physical environment, and the strength of the magnetic field.

The second process is spin-spin relaxation, which is the process by which the transverse magnetisation decays as a function of time. The time constant for transverse relaxation is conventionally termed T2. The transverse relaxation time of solids is very short as they have fixed molecules which maintain local field variations. Transverse magnetisation is maintained for a longer time in liquids. In biological tissues that are visible by MRI, T2 values range from around 1 ms to 1 second. In practice, the free induction decay (FID) decays away faster than would be predicted by T2 processes. This is because of inhomogeneities in the  $B_0$  field cause the local Larmor frequency to vary from location to location, which causes signal dephasing. This more rapid signal loss is referred to as  $T2^*$  decay.

#### **2.4.1.2 The spin echo**

As mentioned previously, following a RF excitation pulse, spins experiencing different local magnetic fields lose phase coherence causing the transverse component of magnetisation to decrease. Although the signal is reduced, the  $T2^*$  effect causes the phases to be dispersed rather than randomised. If another RF pulse is applied that flips the dispersed magnetisation by  $180^\circ$ , those components that are phase advanced will become phase delayed and vice versa. The signal during the pulse sequence changes as follows: i. Following the  $90^\circ$  excitation pulse a FID is generated that decays with time constant  $T2^*$  ii. The  $180^\circ$  pulse refocuses the spins, and the signal is at maximum at time TE iii. The signal decays again as the spins diphas. By applying a  $180^\circ$  pulse every TE, a train of spin echoes is created. The magnitude of the spin echo decays according to T2 due to time varying non-refocusable inhomogeneities. Each echo decays with time constant  $T2^*$  due to static field inhomogeneities.

#### ***2.4.1.3 Image formation and spatial encoding***

In order to form an image, it is necessary to encode the received signal in such a way that its components can be related to the spatial position of nuclei contributing to the signal. The resonant frequency of a nucleus is proportional to the strength of the magnetic field. By applying a magnetic field gradient which either subtracts from or adds to  $B_0$ , the magnitude of  $B_0$  can be adjusted in a linear manner with distance. This makes the precessional frequency vary in a predictable linear way along the direction of the applied gradient and provides a basis for spatial encoding and thus image production.

#### ***2.4.1.4 Frequency encoding***

Following slice selection, it is necessary to locate the signal within the slice, which requires spatial discrimination in two further coordinate axes. The first of these directions is achieved by a process called frequency encoding. Switching on the frequency encoding gradient causes the precessional frequency of nuclei to be altered in a linear fashion, enabling the location of the nuclei along the direction of the gradient to be determined according to its frequency.

#### ***2.4.1.5 Phase encoding***

Localisation of the signal along the remaining axis of the body is described as phase encoding. Once again when this gradient is applied an alteration occurs in the precessional frequency of the nuclei along its axis, resulting in a phase shift. When the gradient is switched off the magnetic field experienced by the nuclei returns to  $B_0$ , but the phase difference between the nuclei remains. In this way, their position along the phase encoding gradient is identified. Because it is only possible to read out with one gradient active at a time (driving two gradients simultaneously simply results in an oblique gradient), phase encoding is achieved in a stepped fashion. After each excitation a specific phase encode gradient is applied, then turned off before signal is recorded during the action of the frequency encode gradient. The phase encode gradient is then incrementally changed over a repetitive cycle of measurements to build up the full encoding required in that direction. The amplitude of the phase encoding determines the remaining dimension of the FOV. If a succession of  $180^\circ$  refocusing pulses is used to create a train of multiple spin echoes, each successive echo can be individually phase encoded and read out with its own frequency encode gradient. This allows data to be acquired more rapidly and is known as a fast spin echo (FSE) approach.

The signals collected during the action of the frequency encode gradients for each phase encode gradient are digitised to form a 2 dimensional array of values that contain information about the distribution of signals within the excited slice. To convert this data into an image a frequency analysis must be performed and this is done using a two-dimensional Fourier transform. The result is an MR image.

## **2.4.2. Sequences used in imaging congenital heart disease**

### ***2.4.2.1 Interactive scanning***

It is common practice in our department to perform a real-time (interactive) MRI at the beginning of each cardiac examination in patients with congenital heart disease. This provides us with a quick impression of the overall anatomy that will help us plan the subsequent examination. Imaging planes are defined and stored, so that they can be used later for the MRI sequences that will be subsequently performed. For example, storing a sagittal plane of the aortic arch and naming it “a.arch” allows us to then use it for sequences such as black blood, cine spin echo loops and phase contrast flows with which we can assess the anatomy and define the inplane velocity across the aortic arch.

The most commonly stored imaging planes during interactive scanning are the following:

4chamber view, RVOT, LVOT, PA-TP, Ao-TP, LPA-TP, RPA-TP, SA, 3D Gadolinium angiogram and 3D SSFP (3D whole-heart). In addition imaging planes such as SVC, IVC, bicaval view etc. can be stored, depending on the requirement to study certain anatomical structures specific to the patient’s anatomy and physiology.

### ***2.4.2.2 Spin echo***

Spin echo sequences use dual inversion to obtain nulling of the signal from the blood, hence the blood pool appears with little or no signal. As a result, the blood in the intracardiac cavities and the great vessel appears black, hence the name „black blood imaging“.

In practice, fast spin echo sequences are used nowadays to provide better nulling using number of signal averages of 1 or more, depending on whether the sequence is obtained during a breathhold or not.

Spin echo sequences can be weighted to T1 or T2 and thus provide information about tissue characterisation, such as in infiltrative cardiac muscle disease (arrhythmogenic right ventricular dysplasia, amyloidosis etc).

#### ***2.4.2.3 Gradient echo***

Gradient echo sequences result in high signal from the blood pool and therefore they are otherwise called „bright blood“ sequences. Gradient echo sequences were used in the past for angiographic MR imaging. The two dominant techniques were: a. time of flight and b. phase contrast. Due to the long acquisition time, gadolinium enhanced angiography has today replaced angiographic MR imaging using gradient echo sequences. Instead, these sequences are very useful in examining the cardiac, vascular and valvar anatomy with great detail as well as obtaining an accurate estimation of ventricular function. For estimation of the anatomy, cine gradient sequences are used. With these sequences, it is possible to acquire a single ECG-gated slice in dynamic fashion with a cine series of images. 20-40 different time frame images can be obtained for each slice in a single breath-hold, depending on the heart rate. Using a transverse stack of slices in the short axis plane through the ventricles, it is possible to estimate the ventricular ejection fraction and the ventricular volumes. In addition, combining the stroke volume of each ventricle with the forward flow in the great vessels (using the phase contrast flow sequences described below), we can derive the degree of valvar regurgitation at the atrioventricular valve level.

More recently, a more modern echo technique called steady state free precession (SSFP) is used to obtain a 3D „whole heart“ analysis. This technique uses steady states of magnetisations. In general, SSFP MRI sequences are based on a low flip angle gradient-echo MRI sequence with a short repetition time (TR), which allows for fast imaging. In cardiac scanning 3D SSFP is acquired during the still period of the heart, either in end-systole or in end-diastole or even in both (dual phase 3D). During the cardiac still period there is no turbulence of flow and therefore no loss of signal, resulting in high resolution images. The 3D SSFP sequence can also be analysed in a way to provide 3D angiography without the use of contrast.

#### ***2.4.2.4 Velocity and flow***

By using an adaptation to the reconstruction algorithm of phase contrast angiograms, velocity component information can be acquired. A subtraction technique is used, so that two images are obtained for each phase of the cardiac cycle. If the slice plane is perpendicular to a vessel (through-plane), summation of the velocities in the vessel repeated for every phase of the cardiac cycle can be used for estimation of blood flow in that vessel. If on the other hand, the slice plane is in the plane of the direction of blood flow (in-plane), then the cardiac phase with the highest velocity pixel can be used to provide an indication of the velocity gradient

across a narrowing. The peak velocity data acquired with a short enough echo time has been found to be accurate in comparison to Doppler echocardiography. Phase contrast through-plane imaging across the short axis of vessels gives accurate flow information, which can be used to calculate intracardiac shunts and quantify the degree of valvar regurgitation.

#### ***2.4.2.5 Three-dimensional contrast MR angiography***

Contrast enhanced MRA angiography has been used for over a decade now to image the great vessels, most commonly the aorta, pulmonary arteries and veins as well as the systemic veins. The timing of acquisition in relation to the contrast administration has to be adapted to target the structures of interest. Arterial and venous phase can be separated well, particularly in lower heart rates. On the contrary, in infants and young children with fast heart rates, the venous and arterial structures may be imaged simultaneously. Similarly, separation of the venous and arterial structures will not hold in patients with intracardiac shunts, such as ventricular septal defects. Real time bolus detection allows more accurate timing of image acquisition but is also useful in recognising differential filling times between the two lungs in patients with unilateral severe pulmonary artery stenosis for example.

The acquired sequence can be post-processed with tools such as maximum intensity projection (MIP) and multiplanar reformatting, to visualise the three-dimensional structures and spatial relationships between vessels. In addition, other image processing techniques, such as volume rendering and surface rendering allow structures of interest to be visualised in a three-dimensional nature.

## **2.5. Aims of Thesis**

The feasibility of performing sole MR-guided diagnostic cardiac catheterisations under interactive real-time MRI was first established in our institution in 2002 <sup>1</sup>. In parallel, a facility incorporating a cardiovascular X-Ray system and a state-of-the-art scanner, called XMR facility, has been developed and used with specific indications. XMR catheterisations were initially employed and validated against standard cardiac catheterisation for the assessment of pulmonary vascular resistance (PVR). In the past few years the indications for XMR catheterisations have widened to include assessment of anatomy and function of univentricular hearts and haemodynamic measurement combined with cardiac output response to pharmacological stress. The combination of X-Ray guided cardiac catheterisation with an

MRI scan can result in the reduction of catheterisation time and fluoroscopy times, because the anatomy is obtained by the MRI scan and not by the performance of contrast angiograms. X-Ray fluoroscopy is therefore used only during manipulation of catheters and wires inside the heart.

The purpose of the research work presented was two-fold: a. to extend the potentials of XMR-guided cardiac catheterisations and address physiological questions (such as response of cardiac output and haemodynamic measurements during pharmacological stress mentioned above) and b. to advance our already established programme of solely MR-guided *diagnostic* cardiac catheterisations in order to materialise the first-in-man solely MR-guided *therapeutic* cardiac catheterisations. In this way, transcatheter interventional procedures were aimed to be performed in the MR scanner in a similar fashion and with similar equipment to the ones used in the traditional catheterisation suite, without the exposure to ionising radiation.

The work towards materialisation of this idea and the world-first clinical trial on solely MRI-guided cardiac interventions for congenital heart disease are being presented in this thesis.

## **2.6. Overview of Thesis and chapter description**

This dissertation is submitted as a “Thesis incorporating publication” according to the King’s College guidelines.

Chapter 3 that follows is word for word our published paper on ‘MR-imaging guided cardiovascular interventions in young children’, published in 2012 in the “*Magnetic Resonance Imaging Clinics of North America*”.

In addition to this publication, chapter 3.4 describes how bridging can occur between XMR-guided *diagnostic* and XMR-guided *interventional* procedures and 3.5 describes the bridging between solely MR-guided *diagnostic* and MR-guided *interventional* cardiac catheterisations giving word for word our publication in *Heart*: “Test Occlusion Of Fontan Fenestration: Unique Contribution Of Interventional MRI.

Chapter 4 describes our research on cardiovascular pre-operative assessment of children prior to liver transplantation using: combined ‘Cardiac Catheterisation and Magnetic Resonance Imaging’ with Dobutamine stress. This is unpublished work on the assessment of cardiac output response of patients with and without fixed right heart obstructions, (such as valvar or branch pulmonary artery stenosis) undergoing pre-liver transplantation work-up.

Evaluation of the XMR catheterisations performed for assessment of PVR was not one of the main aims of this thesis (as this work has been published by other colleagues in our



department previously) and therefore results of these procedures are not presented in this dissertation.

Chapter 5 describes the preparatory research work towards the first-in-man clinical trial on MR-guided cardiac interventions using MR-compatible devices. Assessment of the catheterisation equipment and in particular the fibreglass guidewire that was planned to be used in the MRI environment for the performance of transcatheter interventions was performed in vitro. Assessment of its safety and mechanical properties are described in this section.

Chapter 6 describes the study protocol of the first-in-man clinical trial on MR-guided cardiac interventions using MR-compatible devices; the background & rationale, selection and withdrawal of subjects, as well as the Ethics & Regulatory Approvals are presented in detail.

Chapter 7 is word for word the 3rd published paper of this thesis on „MR-guided cardiac interventions using MR-safe passive devices: a preclinical study and first-in-man congenital interventions “, published in *Circulation Cardiovascular Interventions* in 2010. The pre-clinical animal study as well as the first two clinical patients that underwent interventional catheterisation procedures using sole MRI fluoroscopy are described in this publication.

Chapter 8 describes the results of subsequent patients enrolled in the clinical trial and continuous with a final discussion and future directions.

## CHAPTER 3.

### MR-imaging guided cardiovascular interventions in children

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#### 3.1 Introduction

Congenital heart disease occurs in 0.8-1% of children. A proportion of these patients will require interventional treatment in the form of cardiac catheterisation or surgery, whilst some will only require medical therapy. Echocardiography is the investigation of choice for diagnosis and follow-up of these patients, whilst magnetic resonance imaging (MRI) is now increasingly used in most centres as another non-invasive imaging modality to assess complex congenital cases and to answer specific questions, not possible to address with echocardiography. The complexity of congenital heart disease entities being treated today, as well as the surgical and interventional survival for congenital heart disease has generated questions and necessitated treatment options that were not available in the past. The treatment options and their success have made the paediatric cardiology community re-consider of how best to further investigate, treat and prolong further the survival and quality of life of these patients. Surgical correction of older patients that had been left untreated has been revisited, medical management optimisation with new drugs has become possible and questions such as resulting comorbidities (ie the risk of tumor formation) in multi-catheterised and multi-investigated patients using X-Ray radiation have become relevant. For this reason, diagnostic cardiac catheterisations and CT scans have been replaced by cardiac MRI wherever possible.

A new form of hybrid imaging (XMR) has also been introduced, which combines the use of both X-Ray and MR fluoroscopy during the performance of cardiac catheterisations. XMR can address clinical questions, such as estimation of pulmonary vascular resistance and cardiac output response to stress accurately, without the limitation of haemodynamic assumptions during calculations <sup>1-8</sup>. In addition, when invasive pressure monitoring is required, the combination of MRI with cardiac catheterisation has also been used and proven to reduce the screening time and radiation dose <sup>1</sup>. This is achieved by minimising the X-Ray screening to the absolute minimum in order to obtain information that cannot be otherwise obtained by the MRI scan, whilst questions of anatomy and function are left to be assessed with the MRI study.

Finally, beyond diagnosis, MRI nowadays expands its potentials in guiding interventional procedures that can be potentially performed in the MR scanner in a similar fashion and with similar equipment to the ones used in the traditional catheterisation suite. This chapter discusses in detail how magnetic resonance imaging can be used for interventional diagnosis and treatment in young children with congenital heart disease.

## **3.2 MR-guided diagnostic catheterisations combined with X-Ray imaging**

In the current era, diagnostic cardiac catheterisations have been greatly replaced either by MRI scans or by combined MRI-cardiac catheterisation procedures (XMR catheterisation). The latter have been shown to entail lower radiation exposure doses as compared with controls<sup>2</sup>, which is of particular importance in children with congenital heart disease, who are usually subjected to various and repetitive procedures involving radiation. According to the U.K. National Radiation Protection Board, the mean risk of solid tumor development as a result of a single cardiac catheterisation procedure is approximately 1 in 2500 in adults. This risk increases to 1 in 1000 in children if exposure occurs by 5 years of age<sup>9</sup>. Also, the proportion of the body that is irradiated increases as the size of the patient decreases, and that coupled with the increased radiosensitivity of the young and immature tissues explains recent evidence showing that these children are at higher risk of developing cancer in later life<sup>10-12</sup>.

A further benefit of XMR guided catheterisations is the improved soft tissue characterisation and visualisation of cardiac structures and vessels, in contrast to X-Ray guided catheterisations, which rely on identification of landmarks and contrast angiography. XMR catheterisations also provide physiological data, that are not possible to obtain during X-Ray catheterisation and that are essential for the assessment of complex patients. Such data involve cardiac output assessment, accurate estimation of Qp:Qs, flows and maximum velocities across valves and in large vessels, pressure-volume loop relationships and ventricular function.<sup>13-19</sup> In addition, pulmonary vascular resistance and compliance can be accurately assessed using invasive pressure measurements and MR flow data.<sup>20-23</sup>

### **3.2.1 Equipment**

XMR catheterisations take place in specifically designed catheterisation laboratories with combined X-Ray and MRI facilities (Figure 1-1) or in geographically adjacent cath lab and MRI suites. In our laboratory we use a 1.5T MR-scanner (Achieva, Philips, Best, Netherlands)

and a Philips BV Pulsera cardiac X-Ray unit. There are in-room monitor and controls, which can swing across both the bottom end and the top end of the magnet, and display MRI images and haemodynamic pressure traces (Figure 1-2). The fluoroscopic area and magnetic resonance field of an XMR laboratory can be separated either by doors or by a clearly defined line, demarcating the 5-gauss line of the magnet, beyond which it is possible for electronic devices, such as echocardiography machines and computer equipment, to be brought into the room (Figure 1-1). The tabletop design allows patients to be moved from one modality to the other in a very short time. Furthermore, the table position is stored within the system allowing image fusion between the MRI and X-Ray system or even fusion with other imaging modalities (e.g. echocardiography) <sup>24</sup>.

After the patient is placed on the table in the non-magnetic area of the XMR room, the MRI coil and ECG leads are placed. MR compatible patient monitoring and anaesthetic equipment is used. For pressure monitoring, we use the commercially available haemodynamic monitoring system EP Tracer 102 (CardioTek B.V, Maastricht, Holland). All of the anaesthetic and monitoring tubing and lines are designed with extra length and are secured to the movable tabletop to ensure smooth patient transfer. The ECG and invasive pressure data are sent from the MR-compatible monitoring equipment via an optical network to a computer in the control room, where the cardiac technician is stationed. The appropriate measurement and recording of the data is made in the usual way. The technician has access to monitors that show the appropriate X-Ray or MR images of the procedure. Blood samples taken during the procedure are labeled in the room and passed to the technician in the control room. Monitoring of the cardiac rhythm during XMR catheterisation is achieved with a vector electrocardiogram (VCG). This is a QRS detection algorithm that automatically adjusts to the actual electrical axis of the patient's heart and the specific multidimensional QRS waveform. This greatly improves the reliability of R-wave detection to nearly 100%. A reliable R-wave, with the P- and T-waves that are also always clearly seen with VCG, allows detection of nearly all arrhythmias. Unfortunately, there are no ECG systems that can reliably provide ST segment or T-wave morphologic information. In the future, using signal-processing techniques, it may be possible to improve ECG monitoring during MR scanning.

Lastly, significant consideration has been given in the design, construction, and operation of our XMR facility with regards to safety, and a comprehensive safety protocol has been drawn up in our laboratory to minimize possible hazards (Table 3-1).

**Table 3-1. X-Ray and Magnetic Resonance Facility: Safety Features**

- 
- Compulsory safety training of all magnetic resonance interventional staff
  - Specially designed clothes without pockets
  - Safety officer restricting entry to the main room during XMR intervention
  - Clear demarcation of ferromagnetic safe and unsafe areas within the room
  - Magnetic-resonance-compatible anaesthetic and monitoring equipment
  - Noise-proof headphone systems for all staff within the room
  - X-Ray- and radiofrequency-shielded scrub room
  - Positive pressure air handling and filtration system
  - Tethering of all ferromagnetic equipment to the wall or floor
  - Safety checks whenever a patient is transferred between X-Ray and magnetic resonance to ensure that metallic instruments used for catheterisation are not taken across to the magnetic resonance end of the room
  - Written log of all safety infringements and regular review of safety procedures
- 

### ***3.2.2 XMR catheterisation procedure***

The children are prepared in a similar fashion to the ones undergoing routine cardiac catheterisation. In our department, the patients are anaesthetised and recovered in a dedicated area adjacent to the MRI scanning area. They are wheeled into the MRI room on MR compatible trolleys and the procedure starts with cardiac catheterisation in the non-magnetic field area of the XMR laboratory. The facilities and equipment of the X-Ray area are similar to the traditional catheterisation laboratory. A non MR-compatible angiographic pump is brought into the laboratory and used for detailed angiography, when needed. Standard ECG leads are placed as well as a three-lead ECG attached to the anaesthetic machine and the VCG, to use for cardiac monitoring during MR scanning. The VCG electrodes are placed on the subcostal margin, outside the X-Ray field of view, and the VCG is used for triggering MR scans. An MR-compatible pulse oximeter and noninvasive blood pressure monitoring equipment are also attached. The exhaled anaesthetic gases are monitored for end-tidal carbon dioxide as well as the concentration of the volatile anaesthetic agents. Flexible phase array RF coils are used. These coils are relatively X-Ray lucent and thus do not need to be removed between MR and X-Ray imaging.

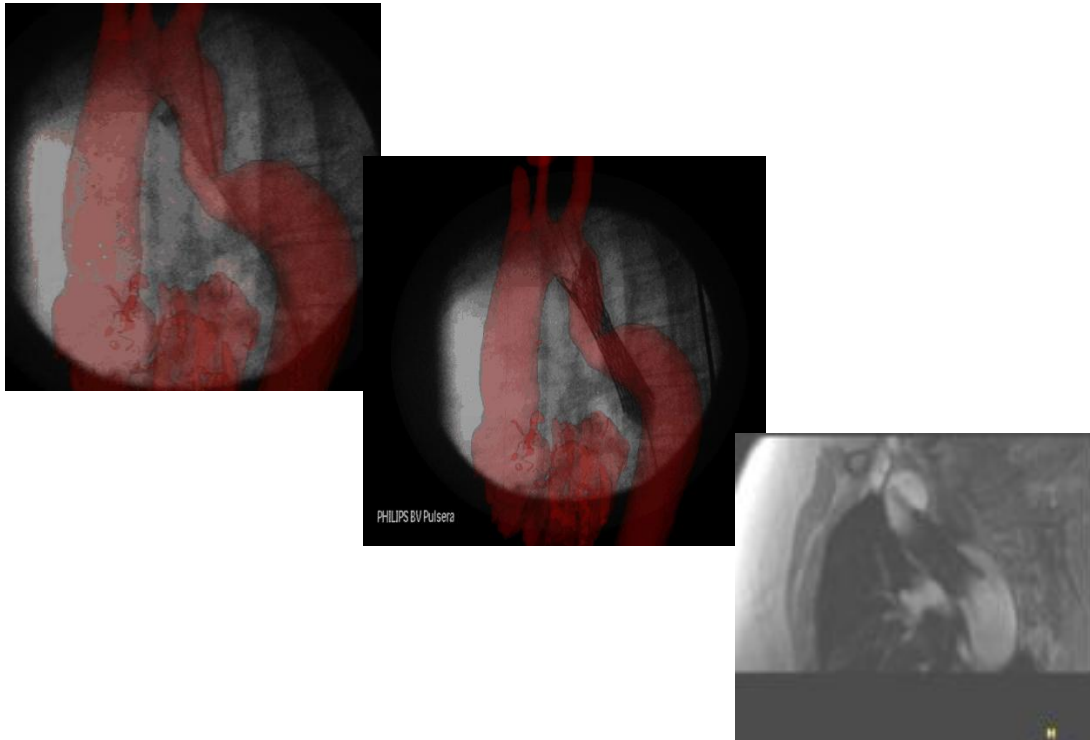
After femoral venous and arterial access is obtained, a heparin bolus of 50IU/Kg is given with ACT monitoring. Once right and/or left heart catheterisation is completed under X-Ray guidance, the patient is moved across to the MRI scanner on the sliding table after the standard ECG leads are removed and safety checks have been performed. These include an

operating theater-style check of all metallic objects used under X-Ray. Once the patient is inside the scanner, a second drape is placed and then lifted up and taped to the top of the magnet, which in effect provides sterile draping of the bore and sides of the magnet (Figure 3-1). MR-compatible catheters (Wedge catheter, Arrow, Reading, PA, USA) placed during fluoroscopic-guided cardiac catheterisation are left in situ, usually in the right ventricle or main pulmonary artery for continuous haemodynamic pressure monitoring. Invasive arterial pressure is monitored through a femoral arterial cannula or sheath. Simultaneous MRI phase contrast sequences or MR-cine scans with pressure recordings are performed. These give the physician a “snapshot” of the patient’s physiology at that particular time and reflect the conditions that they may have been subjected to (ie: nitric oxide administration during PVR assessment or dobutamine stress testing). In addition, a free breathing ECG-triggered three-dimensional (3D) SSFP scan of the heart and great vessels and 3D contrast enhanced MRA are also performed to elucidate intracardiac and vascular anatomy.

We have performed over 150 cardiac catheterisations for congenital heart disease in our XMR laboratory (published abstract: Tzifa A, Bell A. *Cardiol Young*; 2011). Some of these have involved combined X-Ray and MR-guided procedures, whilst others have been performed solely under MR-guidance. Most of the catheterisation procedures were performed for PVR measurement, while a number were performed to define anatomy, perform XMR-guided interventions (Figure 3-2) or assess the cardiac output stress response to Dobutamine.



**Figure 3-1.** Draping of the top of the magnet to ensure sterility inside the MR-scanner.



**Figure 3-2.**

Aortic stent implantation using the XMR guidance system. A magnetic resonance angiography image is superimposed onto the fluoroscopic image during stent implantation for native aortic coarctation with very tortuous aortic arch (a). A bespoke made covered CP stent was implanted across the coarctation in the X-Ray part of the XMR lab (b). Following stent implantation the patient was moved back to the scanner and a repeat MRI study showed good stent position and no areas of dissection.

### **3.2.3 XMR catheterisation for assessment of pulmonary vascular resistance**

Pulmonary vascular resistance studies have been performed either with fluoroscopic or MR-guidance. There is no age limit for the performance of these studies, but higher spatial resolution is required for phase contrast flow imaging in infants to ensure there are enough pixels covering the vessel of interest for accurate flow measurements. With the technique described above, the patient undergoes an MRI scan and phase contrast flow images are obtained in the MPA, RPA, LPA and aorta with simultaneous pressure monitoring. For patients with univentricular heart palliation, flows are assessed in the branch pulmonary arteries for PVR estimation, but also in the two caval veins, the neo-aorta (and native aorta, when of good size) for detailed assessment of the physiology and the flow distribution.

When the PVR at baseline is raised, 100% FiO<sub>2</sub> and nitric oxide 20ppm are given and the PVR is recalculated. It is important to obtain saturation/blood gas at the beginning of the procedure and during different stages of the protocol, as dictated by the patient's clinical condition and end-tidal CO<sub>2</sub>. This is to ensure a steady anaesthetic state and normocarbia,

which is vital for accurate PVR measurement, as the latter can swing and be inadvertently elevated if the CO<sub>2</sub> levels are allowed to rise. Our group has found moderate to good agreement between the Fick method and the MR method of deriving PVR at baseline conditions <sup>1</sup>. However, in the presence of nitric oxide, which is used to assess pulmonary vasoreactivity, there was less agreement between the two methods. There was not only worsening in agreement but also a large bias when PVR was measured in the presence of 100% oxygen and nitric oxide. We believe that this is the result of errors in the Fick method rather than the XMR method, which has important implications for patient management, particularly of young children. To this end, we suggest that PVR measurement in children is performed with the MR method wherever possible.

### **3.2.4 XMR catheterisation for assessment of cardiac output response to stress**

MRI is the ideal tool for the evaluation of cardiac function and output. When combined with dobutamine stress it allows the measurement of RV function, LV function, cardiac output and cardiac output in response to stress and systemic vasodilation. Further to a full anatomical assessment, MRI cardiac catheterisation combined with dobutamine stress enables evaluation of the RV pressure compared to systemic, the RV systolic and diastolic function in response to stress, the gradient across the pulmonary valve or branch pulmonary arteries and the pulmonary artery pressure and pulmonary vascular resistance. If the PVR is elevated, pulmonary vasodilators can be administered and the patient's PVR and haemodynamics are reassessed. Selective angiography can also be performed to address clinical questions, such as pulmonary arteriovenous malformations or abnormal collateral vessels that are not clearly visualised on MRI.

Dobutamine stress study for assessment of the cardiac output response to stress is occasionally performed for clinical or research purposes in selected patients. Suitable groups are children with Alagille syndrome and pulmonary artery stenosis, patients after tetralogy of Fallot repair, or more rarely children with univentricular heart circulation (Published abstracts: Bellsham-Revell H; Tzifa A JCMR 2011).

Our MRI with Dobutamine stress scan protocol is described as follows: We always ensure that the patient is not intravascular dry, as this may affect the cardiac output response to stress. After femoral venous and arterial access is obtained, a heparin bolus of 30-50IU/Kg is given with ACT monitoring. Right heart catheterisation is performed either with fluoroscopic or MRI guidance. Pressure measurements are obtained in the femoral artery, IVC, RA, RV, MPA, LPA (proximal and distal), RPA (proximal and distal), RPA and LPA wedge



or left atrium if an atrial communication is present. An MRI compatible catheter (wedge catheter, Arrow) is left in the RV and an MRI scan is performed. This includes a 4 chamber view, RVOT and LVOT views in two planes, Gad MRA, 3D volume SSFP scan, short axis stack (for LV and RV functional assessment), phase contrast flow images in the aorta and pulmonary artery (for assessment of cardiac output and shunt) and differential branch pulmonary artery flows. The PVR is obtained from PA flow measurement combined with direct pressure measurement, as described above. After baseline data are obtained, dobutamine is infused at 10 micrograms/kg/min and repeat short axis stack and phase contrast flows in the aorta and pulmonary artery are obtained. The infusion is then increased to 20 micrograms/kg/min with repeat short axis stack and phase contrast flows in the aorta and pulmonary artery. We aim for a heart rate increase by > 50% from baseline. After all physiologic measurements have been obtained, the dobutamine infusion is discontinued and the patient is woken up and extubated. Children are observed on the ward for a few hours post anaesthetic and are usually discharged home the same day.

#### *Value of dobutamine stress studies in pre-liver transplantation patients.*

Our group have shown the value of dobutamine stress studies in patients with Alagille syndrome and branch pulmonary artery stenosis <sup>25</sup>. It was concluded that patients with a maximal increase in cardiac output of less than 40% and or right ventricular/aortic pressure ratio of equal or greater than 0.5 should be considered at higher risk and were associated with less favourable outcome following liver transplantation. This study was not performed in an XMR setting, but in the cardiac catheterisation laboratory, using a flow-directed thermodilution catheter and cardiac output calculations were performed on a dedicated computer (Vigalence, Baxter, Newbury, Berkshire, UK). In the current era, MRI can obtain the above calculations easily and with more precision, providing data on the ventricular function and volumes as well as flows across the great vessels, as described in Chapter 4 of this thesis in more detail.

### **3.3 Solely MR-guided diagnostic cardiac catheterisations**

MR-guided cardiac catheterisations have been diagnostic in nature (in humans) and interventional (in animals). Visualisation has been aided by passive and active visualisation techniques and catheter tracking. Passive tracking technique is commonly based on

visualisation of susceptibility artifacts or signal voids caused by the interventional device under MR imaging,<sup>26-29</sup> whereas active catheter tracking and visualisation uses an electrical connection to the MR scanner, and localisation or tracking of the device requires the device itself, along with any additional hardware or software that comes with it. Typically, the device is equipped with a coil or an antenna that functions in either receive-only mode or transmit/receive mode<sup>30-36</sup>.

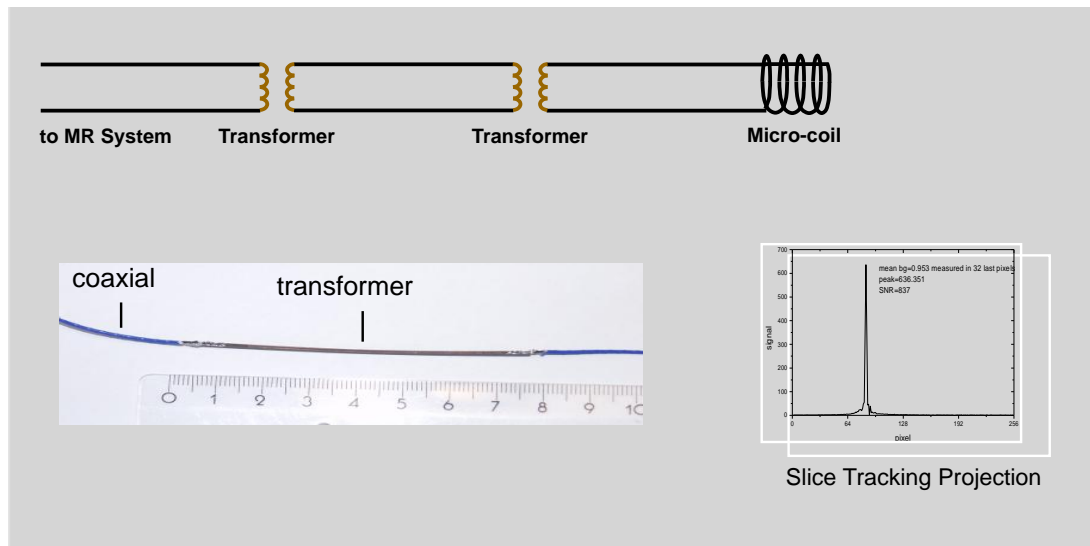
Active guidewires that have been used for MR-guided interventions in animals are tracked or visualised by employing miniature RF-coils or loopless antenna both connected to the scanner using a long metallic wire. This long wire can heat up during certain MRI sequences due to resonating RF waves. Despite modifications to reduce the risk of heating with active devices, under certain conditions heating at the tip can occur up to 70°C with obvious associated risks<sup>37</sup>. New strategies for RF-safe active devices have been proposed including optical transmission and use of transformers to shorten the length of the conducting wire (Figures 3-3 and 3-4),<sup>38-39</sup> however no clinically safe active guidewires had been developed so far. Semi-active catheters use tuned fiducial markers that produce increase MR signal locally without wires connecting to the scanner<sup>40</sup>. There are however issues with miniaturisation and the ability of firmly securing these markers to catheters.

Passive devices, such as the ones used in our lab, have the advantage of no risk of heating and lower cost, but the disadvantage of being less visible than active guide wires and requiring manual tracking and changing of the imaging plane to keep the wire in view. To facilitate better and faster visualisation, the operators in our XMR laboratory use foot pedals (Figure 3-5). With those, the operator can start and stop the interactive scanning independently, and also adjust the imaging plane and slice position in order to get the interventional devices in view. The latter is achieved with the foot pedal function, which rotates through pre-selected imaging planes and the pedal pull/push action.

At the beginning of any MR-guided catheterisation, the likely imaging planes needed for subsequent catheter tracking are stored along with the rest of the MRI protocol (Figure 3-6). For example, for right heart catheterisation, the following views are stored: SVC/IVC sagittal and coronal, 4-chamber, RVOT, R2CH, PA bifurcation, LPA sagittal and RPA coronal views. The patients are placed on the X-Ray table, where sheaths are inserted after securing the chosen MRI coil and placement of the VCG leads. The patient is then moved into the scanner and the cardiac catheterisation is performed under sole MRI guidance (Figure 3-7). The in-room consol displays the haemodynamic pressures on one panel and four chosen imaging planes on the other (Figure 1-2). An interactive SSFP sequence (8 to 10 frames/sec)

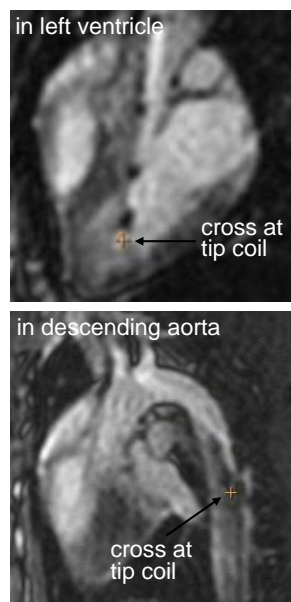
with real-time manipulation of scan parameters is used. The operators can start and stop the MRI scan independently with foot pedals and rotate through the four imaging planes displayed. The balloon wedge pressure catheter is inserted into the sheath in the right femoral vein and advanced into the inferior vena cava (Figure 3-8, 3-9). For this manoeuvre, a para-sagittal imaging plane, showing the inferior and superior vena cava and the right atrium is used. The balloon of the wedge pressure catheter is visualised as a dark signal void within the surrounding bright blood (Figure 3-8). As soon as the right atrium is reached, the imaging plane is interactively changed to show the right atrium and right ventricle from different projections (R2 chamber or 4-chamber view). The tricuspid valve is passed and the balloon wedge pressure catheter is advanced into the right ventricle. The imaging plane is then changed to show the outflow tract and then the main pulmonary artery. The catheter is advanced into both branch pulmonary arteries and the wedge position for detailed pressure measurements with pullback gradient recordings as necessary (Figure 3-9). Because only the tip of the wedge catheter is visualised, care is taken not to push the catheter too fast and thus beyond the MR imaging plane. This also ensures that the catheter does not accidentally form loops and possible knots.

For left heart catheterisation, the balloon wedge pressure catheter is introduced via the femoral artery, inflated with CO<sub>2</sub> and advanced through the descending aorta to the aortic arch. For this step a para-sagittal imaging plane is chosen, which shows the aortic arch, the ascending aorta, the aortic valve and the left ventricle. The balloon of the wedge catheter is visible in the aorta as a signal void. Subsequently, the catheter is turned into the ascending aorta. For this, the use of an MR-compatible guidewire may be necessary, as the balloon wedge catheter at this point tends to travel up the head and neck vessels rather than down to the ascending aorta. Under MR-guidance it is then possible to cross non-stenotic aortic valves in order to measure LV pressure. If catheter manipulation into a particular heart chamber or vessel using MR guidance alone is difficult, the patient is transferred back to the X-Ray end of the room, where catheterisation can be continued under X-Ray fluoroscopy (e.g., to use a guidewire or a braided catheter). The patient can be transferred back to the MR scanner for further MR measurements once the catheter is positioned satisfactorily. The post-catheterisation care is exactly the same as with the routine catheterisation in the X-Ray laboratory.



**Figure 3-3.**

Concept of the transformer-based cable for RF-safety: a) Transformers split a long cable into several short not resonant and thus RF-safe sections. b) Miniature transformer (diameter 1 mm) and coax-cable can be integrated into a catheter lumen. c) Tracking signal with high signal-to-noise ratio allows reliable and RF-safe catheter tracking (data courtesy of Steffen Weiss, Philips Research Laboratories).



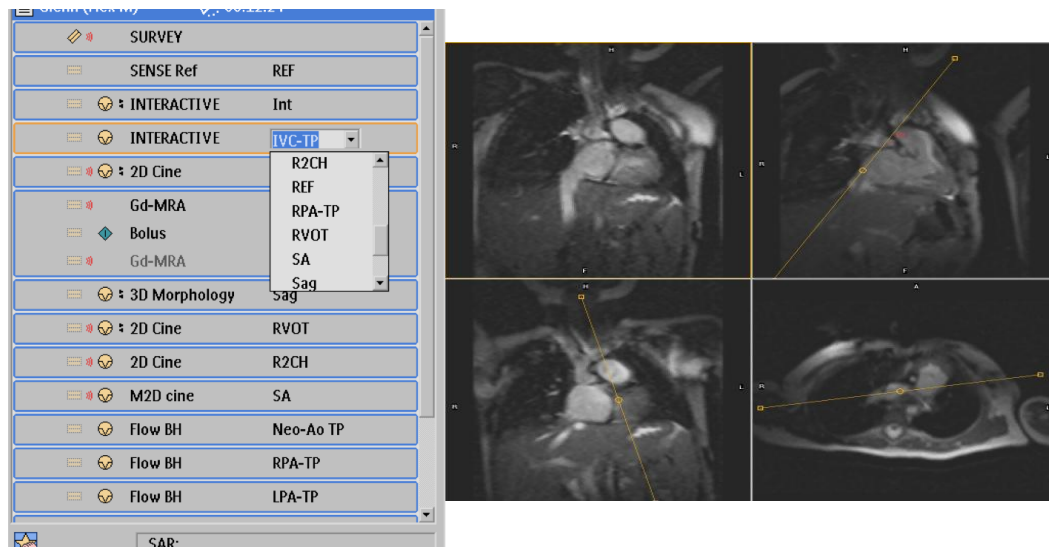
**Figure 3-4.**

RF-safe catheter tracking in a pig experiment. The position of the micro-coil attached on the catheter tip is measured and displayed (cross) on real-time MR images (data courtesy of Steffen Weiss, Philips Research Laboratories).



**Figure 3-5.**

Foot pedals are used to control the real-time MRI interface, e.g. to start/stop real-time MRI and to change between different pre-defined geometries.



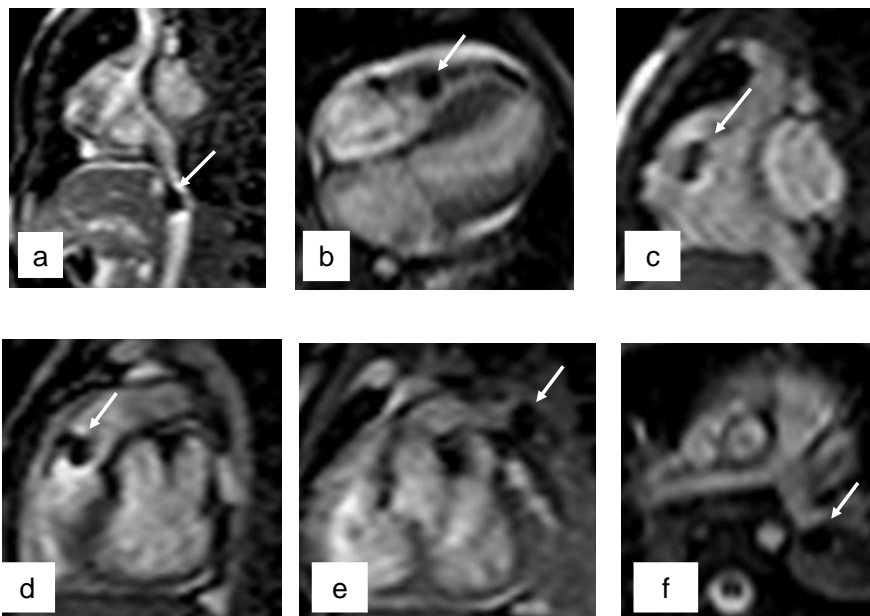
**Figure 3-6:**

Planning and storing of imaging planes needed for subsequent visualisation of the MR-guided catheterisation. Four imaging planes can be put up at a time for the operator to rotate through during MR-guided catheterisation.



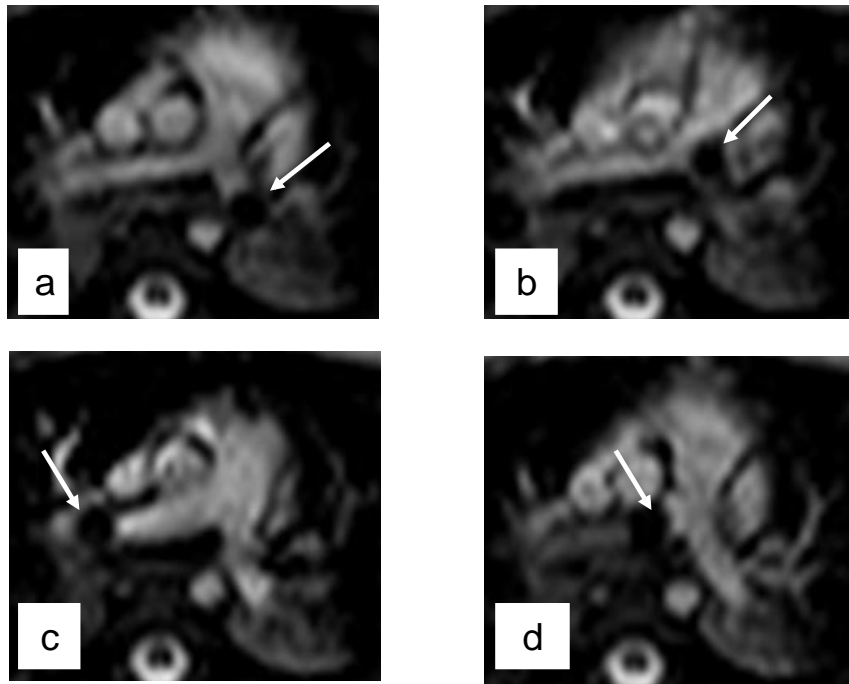
**Figure 3-7.**

Clinical MR-guided intervention. After positioning the patient on the XMR-table (a), the sheaths are inserted outside the MR-scanner (b). The patient is then moved into the MR-magnet and the cardiac catheterisation is completely performed under MR-guidance (c)



**Figure 3-8.**

The balloon of the wedge pressure catheter is visualised as a dark signal void within the surrounding bright blood in the IVC (a), right ventricle (b and c), right ventricular outflow tract (d), distal left pulmonary artery in sagittal (e) and axial view (f).



**Figure 3-9.**

The balloon wedge catheter is advanced into both branch pulmonary arteries and pullback gradient recordings are taken as necessary from LPA distal (a) to LPA proximal (b) and RPA distal (c) to RPA proximal (d).

### **3.4 Bridging between XMR-guided diagnostic and XMR-guided interventional procedures**

Hybrid approaches are becoming increasingly common in the management of congenital heart disease. Combining data from two or more imaging methods has the potential of targeting complex congenital heart disease in the best possible way, with reduced screening time and increased safety and efficacy.

During our XMR catheterisations, image overlay has been used in selected cases, in a way whereby magnetic resonance angiography image has been superimposed onto a fluoroscopic image for better localizing and tracking of a pathological lesion (Figure 3-2).

In congenital heart disease this has been particularly useful for hybrid imaging of aortic arch pathology. As part of this research thesis, eight patients with borderline aortic arch coarctation (native or re-coarctation) underwent MR-assisted cardiac catheterisations to assess the anatomy but also measure gradients across the coarctation at rest and stress with Isoprenaline boluses (Published abstract: Valverde I,...Tzifa A...; Beerbaum P. JCMR 2011). In 6 patients conservative management was followed, whereas one patient underwent surgical

repair and one underwent percutaneous aortic arch stenting. This last patient had a complex aortic arch anatomy with severe tortuosity and needed stent implantation with a bespoke length stent of 6cm. Due to the high risk of the procedure it was decided to perform the intervention in the X-Ray area of the XMR lab, so that the MRI facilities could be used for the pre- and post- implantation assessment. The aortic stent was implanted using the XMR guidance system with simultaneous image overlay, which provided us with more precision during stent placement (Figure 3-2). A magnetic resonance angiography image was obtained first with gadolinium bolus and was then superimposed onto the fluoroscopic image. The bespoke made covered CP stent was implanted across the coarctation in the X-Ray part of the XMR lab. Following stent implantation the patient was moved back to the scanner and a repeat MRI study showed good stent position and no areas of dissection on the black blood imaging.

### **3.5 Bridging between solely MR-guided diagnostic and MR-guided interventional cardiac catheterisations: Test Occlusion Of Fontan Fenestration: Unique Contribution Of Interventional MRI**

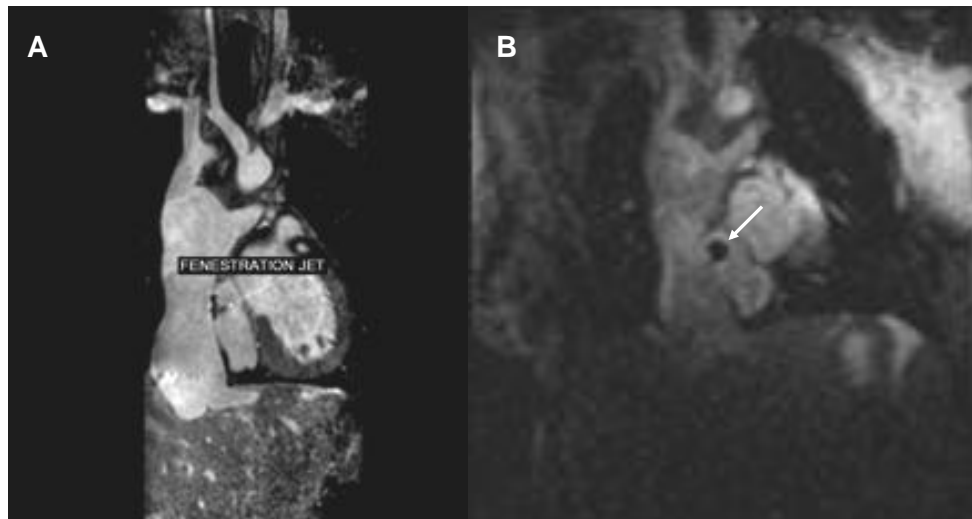
Experience on solely MRI-guided diagnostic cardiac catheterisations and the precision of measured cardiac output changes obtained during those studies led us to further expand the potential of MR-guided cardiac catheterisation procedures. This is for example represented in the following published report of a 24-year old lady with fenestrated Fontan circulation who was referred for combined cardiac MRI and catheterisation procedure. The indication for an XMR study was to assess her anatomy and suitability for fenestration closure. The patient was considering pregnancy, however due to low saturations of 83%, successful pregnancy was unlikely.

Under interactive screening, the balloon of a wedge catheter was inflated in the lateral tunnel to render it visible as a dark spot in the bright surrounding blood. The balloon was then deflated and advanced through the 4mm fenestration (Figure 3-10, Panel A) into the atrium. Atrial saturations measured 83% and aortic phase contrast flow images revealed cardiac output of 3.22 l/min. The balloon was then inflated against the atrial wall to completely obstruct the fenestration (Figure 3-10, Panel B). Repeat atrial saturations measured 96% and cardiac output decreased to 2.95l/min. Lateral tunnel and systemic pressures remained



unchanged. The minor drop of the cardiac output with the balloon inflated represented the contribution of the fenestration flow to the total cardiac output.

Test occlusion of the Fontan fenestration must always be performed prior to interventional closure. In the catheterisation laboratory this entails measurement of the right atrial, left atrial and aortic pressures, mixed venous and aortic oxygen saturations, measurement of whole-body oxygen consumption, systemic blood flow, systemic oxygen transport, and oxygen extraction <sup>41</sup>. However, these measurements can be laborious and prone to errors. This clinical case was representative of a more simplified method of assessing those patients, providing more accurate information on cardiac output changes with simultaneous pressure measurements, and without the exposure to ionising radiation.



**Figure 3-10.**

Panel A: 3D SSFP coronal view of the lateral tunnel showing the Fontan fenestration jet. Panel B: Under interactive imaging, the balloon of the wedge catheter appeared like a dark circle in the surrounding white blood in the atrium (arrowhead). The balloon was kept inflated against the wall to obstruct the fenestration, whilst aortic phase contrast flows were performed to measure changes in the cardiac output

## CHAPTER 4.

### **Cardiovascular pre-operative assessment of children prior to liver transplantation using: combined Cardiac Catheterisation and Magnetic Resonance Imaging with Dobutamine stress**

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#### **4.1 Introduction**

Liver transplantation is occasionally required in children with Alagille syndrome (AS) and biliary atresia (BA). These liver diseases are associated with congenital heart disease in 85% and 15% of cases respectively and are associated with higher liver transplantation (LT) mortality and LT failure. The increased transplant mortality may involve insufficient cardiac output reserve required to maintain adequate systemic blood pressure during and after liver graft reperfusion. Predictive features are peripheral pulmonary artery stenosis, right ventricular hypertension, high RV to femoral artery pressure ratio and low cardiac reserve during dobutamine stress <sup>25</sup>. Our group has previously shown that LT mortality in children with AS is reduced if an increase in cardiac output of > 40% from baseline is induced by dobutamine stress, when cardiac output is estimated by cardiac catheterisation using the Fick dilution technique.

Meticulous preoperative cardiovascular assessment is mandatory in children with CHD who are being considered for LT. This has been traditionally performed by echocardiography, and/or invasive cardiac catheterisation. Neither technique yields three-dimensional (3D) information, and may be limited by sonographic windows or poor soft tissue visualisation, whilst prolonged cardiac catheterisation procedures can be associated with high exposure to ionizing radiation. Furthermore, cardiac catheterisation alone may lead to an inaccurate calculation of the cardiac output and vascular resistance due to physiological assumptions <sup>3,4</sup>.

During this research work, we modified our catheterisation protocol for evaluation of pre-LT suitability <sup>25</sup>, by replacing part of the X-Ray cardiac catheterisation procedure by magnetic resonance imaging (XMR).

## **4.2 Methods**

### **4.2.1 Patients**

Between June 2007 and May 2011, 17 children with liver disease were referred for invasive cardiovascular assessment as part of their assessment for LT (mean age and weight of  $4.7 \pm 4.4$  years and  $14.5 \pm 9.6$  kg, respectively). The diagnosis of liver disease was made on the basis of clinical, radiological and histopathological findings. The study was approved by the local institutional review board and informed consent for dobutamine-stress XMR investigation was obtained from all patients or guardians. A total of 23 XMR investigations were performed. Six patients were found to have obstructive right heart lesions and underwent therapeutic cardiac interventions. XMR procedures were repeated after their anatomy was corrected.

### **4.2.2 XMR Dobutamine stress protocol**

The XMR studies were performed in our combined MRI/cardiac catheterisation interventional suite (Figure 1-1). All patients underwent routine general anaesthesia. Three different conditions were used during the XMR examination: condition I (baseline, resting condition) and two stress conditions, condition II (dobutamine 10 mcg/kg/min) and condition III (dobutamine 20 mcg/kg/min). A steady state was achieved in all patients by 10 minutes in each condition and the following full set of measurements were recorded: Invasive pressure measurements (RV, PA and FA), phase-contrast MRI flow (in the aorta and PA), 2D-cine volumetry (right and left ventricle), electrocardiogram, pulse oxymetry ( $\text{SaO}_2$ ) and end tidal  $\text{CO}_2$ . Cardiac index ( $\text{l/min/m}^2$ ) calculations were performed using phase-contrast flow MRI measurements in the aorta and main PA and analysed using commercially available software (Extended MR Workspace version 2.5.3.1, Philips Medical System, Best, The Netherlands). Pulmonary vascular resistance index (PVRI) was calculated as  $\text{PVRI} = (\text{PA pressure} - \text{PA wedge pressure}) / \text{Indexed PA flow}$ .

## **4.3 Statistics**

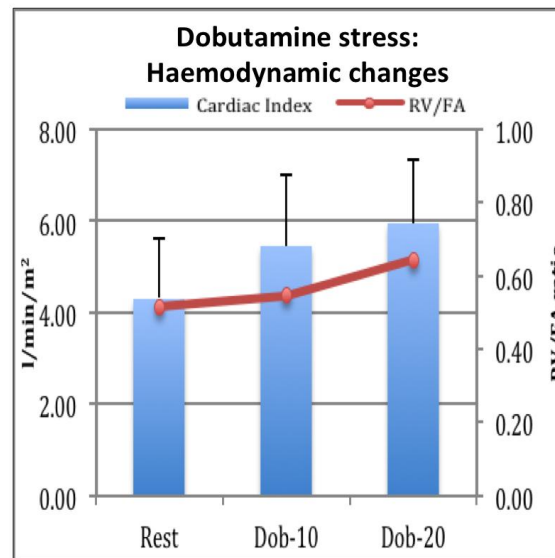
Statistical analysis was performed by using SPSS software (version 18; Chicago, Ill). An ANOVA test was performed to evaluate the haemodynamic changes between the different conditions. A Pearson test was used to analyze the correlation trend. The receiver operator characteristic (ROC) curve of the baseline cardiac index and the maximal percentage increase

in cardiac index during dobutamine were performed. Statistical significance was inferred at  $p < 0.05$ .

## 4.4 Results

Combined XMR was completed successfully in all 23 procedures. A major complication was observed in one patient who developed transient ventricular fibrillation in condition III with dobutamine 20 mcg/kg/min; this reverted promptly to sinus rhythm after discontinuing the dobutamine infusion.

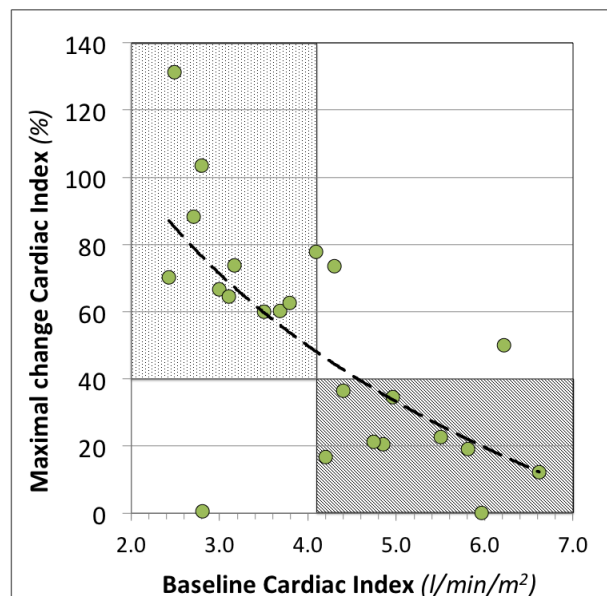
Mean X-Ray screening time and radiation dose were  $8.2 \pm 4.4$  min and  $2.2 \pm 1.9$  Gy $\text{cm}^2$ , respectively. The individual haemodynamic changes during dobutamine infusion are summarised in Table 2-1. There was a significant increase in the heart rate, cardiac index, RV systolic, mean PA and mean FA pressures from baseline to maximal dobutamine (20 mcg/kg/min) stress ( $p < 0.05$ ). The mean baseline heart rate ( $89 \pm 15$  bpm) and cardiac index ( $4.3 \pm 1.3$  l/min/m<sup>2</sup>) significantly increased ( $p < 0.05$ ) at each pharmacological condition. This upward trend in the cardiac index can also be expressed as percentage (%) change above baseline; increasing from condition I (rest) to condition II (dobutamine 10 mcg/kg/min) by 31.4% ( $p < 0.05$ ); increasing again from condition II to condition III (dobutamine 20 mcg/kg/min) by 15.9% ( $p < 0.05$ ) and total increase from rest to the maximal stress change (irrespective of condition) of 48.1%, ( $p < 0.05$ ) (Figure 4-1). The RV/FA ratio significantly increased from condition I ( $0.52 \pm 0.18$ ) to condition II ( $0.55 \pm 0.24$ ) and again to condition III ( $0.65 \pm 0.26$ ). We found a 48% increase of the mean cardiac index from rest to maximal stress state. In 9 of 23 XMR studies, the cardiac index did not rise to above a 40% threshold. However, these patients were already in a hyperdynamic state at rest according to published criteria<sup>42</sup> with a resting cardiac index of  $5.1 \pm 1.1$  l/min/m<sup>2</sup> and a heart rate of  $95 \pm 17$  bpm. The relationship between the cardiac index at rest and its maximal % increase during dobutamine stress was analysed and plotted in Figure 4-2.



**Figure 4-1.**

Bar and line chart haemodynamic changes at rest and during dobutamine stress.

The changes in the cardiac index (bars, units in left axis, standard deviation represented in error bars) and right ventricle to femoral artery ratio (RV/FA) trend is shown in the right axis.



**Figure 4-2.**

Scatter-plot graph for baseline cardiac index (rest) and maximal change in the cardiac index during dobutamine stress. The correlation trend is also shown (dotted line).

There was a significant strong negative correlation (Pearson correlation coefficient - 0.64,  $p<0.05$ ), trend-line shown in Figure 4-2. Those patients with higher cardiac index at rest state displayed less capacity to further increase the cardiac index at the maximal pharmacological stress dose. The ROC curve analysis was performed to identify a threshold for the baseline cardiac index to predict the likelihood to increase in the cardiac index above the recommended 40%. From this analysis, if the resting cardiac index was already above  $4.3 \text{ l/min/m}^2$ , the predicted maximal increase in the cardiac index was unlikely to reach the 40% threshold with a sensitivity of 85% and a specificity of 90% (ROC,  $p<0.05$ ).

The response of the RV systolic, mean PA and mean FA pressures to increasing dose of dobutamine is detailed in Table 4-1.

**Table 4-1. Cardiovascular haemodynamic changes with dobutamine stress infusion.**

Condition	Heart rate (bpm)	Cardiac index ( $\text{l/min/m}^2$ )	RV systolic pressure (mmHg)	Mean PA pressure (mmHg)	Mean FA pressure (mmHg)	Ratio RV/FA
I: Rest	89 (15)	4.3 (1.3)	40.9 (11.5)	20.3 (4.4)	55.4 (12.7)	0.52 (0.18)
II: Dobutamine 10mcg/kg/min	103 (15)	5.5 (1.5)	56.3 (21.2)	25.4 (6.2)	66.2 (13.6)	0.55 (0.24)
III: Dobutamine 20mcg/kg/min	129 (18)	6.0 (1.4)	65.5 (27.9)	26.6 (11.2)	66.6 (15.4)	0.65 (0.26)

A significant change was found in all the previous parameters from rest to dobutamine 20 mcg/kg/min ( $p<0.05$ ). As a consequence, the RV/FA ratio significantly increased from rest ( $0.52\pm0.18$ ) to dobutamine 10 mcg/kg/min ( $0.55\pm0.24$ ) up to dobutamine 20 mcg/kg/min ( $0.65\pm0.26$ ).

Five patients unable to raise their cardiac output above the previously recommended level of 40% due to right heart obstructions underwent 6 interventions (transcatheter  $n=4$ , surgical  $n=1$  and medical  $n=1$ ) and were restudied with XMR post-intervention. All patients that underwent anatomical optimisation (balloon dilation or stent implantation in the RVOT and stent implantation in the branch pulmonary arteries) were capable of raising their cardiac index following physiological stress on repeat XMR catheterisation.

Overall 9 of 17 patients underwent successful LT (age  $6.0 \pm 5.4$  years,  $16.8 \pm 12.6$  kg). One patient was already in a hyperdynamic state at baseline (cardiac index (CI) =  $4.96$  l/min/m<sup>2</sup>) and despite not achieving the previously recommended risk threshold of  $>40\%$  CI increase on dobutamine stress, he was judged suitable for LT and survived.

## 4.5 Discussion

This study represents our modified protocol for evaluation of pre-LT suitability, by replacing part of the X-Ray cardiac catheterisation procedure by magnetic resonance imaging (XMR). In our previous publication <sup>25</sup>, we showed that a maximal increase in cardiac output of less than 40% after dobutamine and/or RV/FA ratio of equal or greater than 0.5 are considered to be at higher risk for LT. In addition, pre-transplant cardiac intervention for main or branch PA stenosis should be considered prior to the LT procedure.

Our practice incorporating MRI has been modified for two reasons:

1. XMR provides accurate measurement of pulmonary flow and cardiac output changes, whilst simultaneously providing intracardiac blood pressure measurements in one sitting. Traditional paediatric cardiac catheterisation techniques for flow quantification are based on the Fick principle using thermo or indicator-dilution methods or the assumed or measured oxygen consumption. These techniques suffer from significantly reduced reliability from an accumulation of errors from multiple measurements and from the presence of intracardiac shunts in children with CHD <sup>3,4</sup>. As an alternative, velocity encoded phase-contrast MRI, which has previously been shown to measure the cardiac output accurately <sup>15</sup> can be combined with invasive pressure measurement to derive accurate pulmonary vascular resistance values <sup>43</sup> and assess the patient's physiology with more precision.
2. MRI gives us high definition imaging and 3D assessment of any anatomical lesions to be targeted and corrected prior to liver transplantation. This is particularly important in patients that require stent implantation in the branch pulmonary arteries, as MRI is the best investigation to plan the procedure in terms of number of required stents, diameters and awareness of neighbouring structures during stent implantation.

The haemodynamic results of our study are consistent with the established pharmacological actions of dobutamine, with significant increases in the heart rate, cardiac index, mean PA pressure, mean FA pressures and RV/FA ratio. As shown in the negative

trend-line correlation (Figure 4-2), those patients with higher cardiac index at rest, probably reflecting the physiological consequences of the severity of their liver disease, displayed less capacity for a further increase at the maximal dobutamine dose. XMR evaluation at rest could therefore be used to predict the ventricular response to dobutamine stress. A resting cardiac index of  $> 4.1 \text{ l/min/m}^2$  could predict an inability to increase the cardiac output by  $>40\%$  during maximal pharmacological stress with a high sensitivity (85%) and specificity (90%). We hypothesise that for patients already in a high baseline cardiac output, it may not be physiologically possible to increase the cardiac output even further above the known 40% threshold<sup>25</sup>. To this end, two children with high basal cardiac index at rest who were not able to increase the cardiac index by greater than 40% were nonetheless considered suitable for LT. Indeed one of these two cases underwent successful LT, whilst the other patient was removed from the transplant list due to improved clinical status.

This is of course supplemental information to our initial statement regarding the suboptimal outcomes in patients with CO increase  $< 40\%$ . To this end, further studies are required to confirm if children with a suboptimal increase in the cardiac index during dobutamine stress should be reconsidered for transplantation, specifically in the setting of supranormal cardiac index at rest, as it happened in the case of the two patients mentioned above.

## **4.6 Limitations**

The main limitation of this study is that it was not powered to determine whether patients with high cardiac output at baseline -and therefore inability to raise their cardiac output above the previously recommended level of 40%- , would still be suitable for transplantation. We hypothesise that this would be the case, but further studies with larger number of patients are required to provide this evidence.

## **4.7 Conclusions**

We conclude that dobutamine-stress XMR is a feasible one-stop investigation for the pre-operative assessment of children who are on the list for LT. The benefits of this hybrid method comparing with the routine catheterisation technique are: a) the provision of all



anatomical data necessary for planning the procedures required for the correction of anatomical obstructions and b) accurate evaluation of the cardiac reserve at rest and stress in order to assess the patient's suitability for LT and evaluate the peri-transplantation risk associated with the congenital heart disease.

## CHAPTER 5.

### **MR-guided cardiac interventions using MR-compatible devices: preparatory research work towards the first-in-man clinical trial**

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#### **5.1 Introduction**

Although, MR-guided diagnostic catheterisations have been feasible without the use of a guidewire, transcatheter interventions nearly always require a suitable guidewire to aid and support the procedures. Standard guidewires, approved for X-Ray procedures, are manufactured from Nickel-Titanium superelastic memory alloys (Nitinol) or stainless steel. Due to the conductive properties of these materials and the length of the guidewire, radiofrequency (RF) coupling can cause significant heating of the material<sup>37</sup>; hence metallic guidewires are not applicable for MR-guided interventions in patients.

Since 2001 there have been a number of animal studies showing the safety and efficacy of interventional MRI (i-MRI) for a multitude of procedures that are currently performed under X-Ray guidance<sup>44-58</sup>. In particular, i-MRI has been used to facilitate procedures such as creation or closure of atrial septal communications<sup>44-47</sup>, intracoronary imaging<sup>48</sup> as well as balloon angioplasty and stent implantation in coronary and carotid arteries<sup>49-53</sup>, stenting of pulmonary arteries<sup>54</sup>, stenting of aortic coarctation<sup>55,56</sup> and vena cava interventions<sup>57,58</sup>. The procedures have been aided by the use of non MR-safe active guidewires and prototype or commercially available devices and were either solely MR-guided or combined with conventional catheterisation before and after the procedure.

The guidewires used for the above interventions were either active or passive. Active guidewires are tracked by in situ miniature RF-coils or loopless antenna both connected to the scanner using a long metallic wire. This long wire can have standing currents induced in it during certain MRI sequences, which can lead to heat generation. Despite modifications to reduce the risk of heating with active devices, under certain conditions heating at the tip can occur up to 70°C with obvious associated risks<sup>37</sup>. Furthermore, active devices are more costly due to hardware modifications. New strategies for safe active devices have been proposed including optical transmission and use of transformers to shorten the length of the conducting wire<sup>38,39</sup>, however, no safe active guidewires have been developed so far. Semi-active catheters use tuned fiducial markers that produce increase MR signal locally without wires

connecting to the scanner <sup>40</sup>. There are however issues with miniaturisation and the ability of firmly securing these markers to catheters. Passive guide wires have the advantage of no risk of heating and lower cost, but the disadvantage of being less visible than active guide wires and requiring manual tracking and changing of the imaging plane to keep the wire in view.

Left heart MR-guided cardiac interventions have also been performed without the use of a guidewire in the LV, in an animal model for transcatheter implantation of a prosthetic valve in the aortic valve position <sup>59</sup>, where the use of susceptibility markers enabled precise position monitoring of the interventional instrument and in patients who underwent balloon dilation of aortic coarctation <sup>60</sup>. In the last study, the procedures were performed in a pilot group of 5 patients and were preceded and followed by conventional catheterisation to assess the arch angiographically and measure pressure gradients across the coarctation segment. A non MR-safe guidewire was used for this purpose. The wire was withdrawn before the patient entered the MR scanner and another self-made non-metallic guidewire was advanced just up to the distal port of the balloon catheter and the procedure was completed under MR guidance. Although the desired result of procedural and haemodynamic success was achieved nearly in all patients without the use of a guiding wire for the valvuloplasty balloon, most teams performing congenital interventions would consider its use mandatory. This provides them with a railroad for catheters and interventional devices to track on, stability during the intervention but most importantly with security of being able to re-cross the lesion should that become necessary in the event of procedural complications.

As derived from the above, the performance of MR-guided interventional procedures using a guidewire that is fully MR compatible and RF safe and has mechanical properties similar to the standard nitinol or stainless steel guidewires had not been possible to date.

In order to facilitate the materialisation of such interventions, an MR-compatible and safe guidewire had to be manufactured. After years of research work a guidewire with the mechanical features of a standard nitinol guidewire was developed and proposed <sup>61</sup>. This was the first guidewire that fulfilled all prerequisites to become a clinical device. The wire underwent robust testing as described below. Further to that, as a pre-clinical step, we used the guidewire in combination with already available MRI safe catheters in an animal model and tested its properties and the feasibility of performing cardiac interventions.

## **5.2 Assessment of the catheterisation equipment to be used in the MRI environment for the performance of transcatheter interventions**

### **5.2.1 Cardiac catheters**

Cardiac catheters should be non-braided in order to be used in the MRI environment. Swan-Ganz (wedge catheters - endhole) or Berman (sidehole) [Arrow, Reading, PA, USA] have been used for the solely MRI-guided catheterisations in our department. Most frequent diameters have been the 4, 5 and 6 Fr. The 4Fr catheters are compatible with a 0.018 guidewire, whilst the 5Fr are compatible with a 0.025 guidewire, hence they would not be suitable to be used for interventions with the proposed guidewire, which was 0.035''. To this end, only 6 and 7Fr wedge catheters were suitable to be used as guide catheters for the MR-guided cardiac interventions.

### **5.2.2 Valvuloplasty balloons**

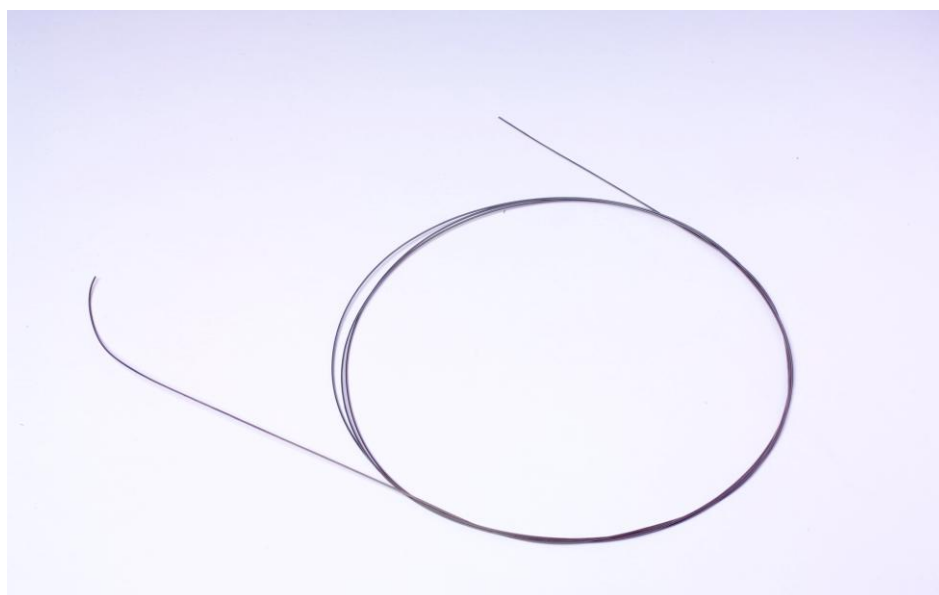
Similar to the cardiac catheters, valvuloplasty balloons should also be non-braided, and 0.035'' guidewire compatible, in order to be used in the MRI environment. The most frequently used valvuloplasty balloons for congenital heart disease (Tyshak valvuloplasty balloons, NuMED, NY, USA), commonly employed for balloon dilation of valves and vascular stenosis are non-braided, hence they could be safely used in the MRI environment. In addition, prior to the first-in-man clinical trial on MR-guided interventions, enquiries were made regarding other non-braided balloons and it was concluded that the Cristal balloons (Bard, Tempe, AZ, USA), do not have any inner braiding, hence they could also be used for valvuloplasties, angioplasties and stent implantations performed under MRI-guidance.

### **5.2.3 MRI-compatible guide wire**

As mentioned above, the newly developed fibreglass guidewire<sup>61</sup> underwent robust testing in vitro prior to testing its performance in MRI-guided cardiac interventions in animals. The testing took place according to the American Society for Testing and Materials (ASTM) – (Appendix).

The wire's length was 220cm and the diameter 0.89mm. The guide wire consisted of a Microscale Pultrusion Material core, composed of fibers of different non-metallic materials, such as quartz. The core material was connected to a Nitinol radio opaque tip. It was coated with Polyvinylpyrrolidone, which is a commonly used hydrophilic coating material in medical

devices. The guide wires were sterilized with Ethylene Oxide and packaged sterile for the clinical trial.



**Figure 5-1.** Fibreglass MR-safe and compatible wire

### **5.3 Assessment of the fibreglass guidewire to be used in the MRI environment for the performance of transcatheter interventions**

Robust assessment of the guidewire's properties took place prior to its use in vivo. The essential requirements checklist demonstrating how the investigational device (fibreglass guidewire) complied with each of the relevant Essential Requirements, as well as the risk analysis are given in the Appendix.

Below is a summary of the most vital testing that the wire underwent prior to getting approval by the UK Medicines and Healthcare Regulatory Authority (MHRA) as a new medicinal device.

#### **5.3.1 Mechanical strength Testing**

##### ***5.3.1.1 Testing method for bending stress***

In a bending assembly the guide wire was bended in 20 cycles around two cylinders with a diameter twenty times as tall as the guide wire. In addition, the guidewire was tested

for resistance against damage caused by bending. The testing assembly consisted of two pivoted cylinders with a diameter of 15 mm, which were mounted with a gap of two millimeters to a plate. Figure 5-2 shows the testing assembly. The guide wire was induced to the assembly and manually bended. This procedure was repeated 20 times in a sequence of cycles. No damages on the guide wires were found. The specifications were according to the DIN-norm.



**Figure 5-2.** Assembly for bending stress testing

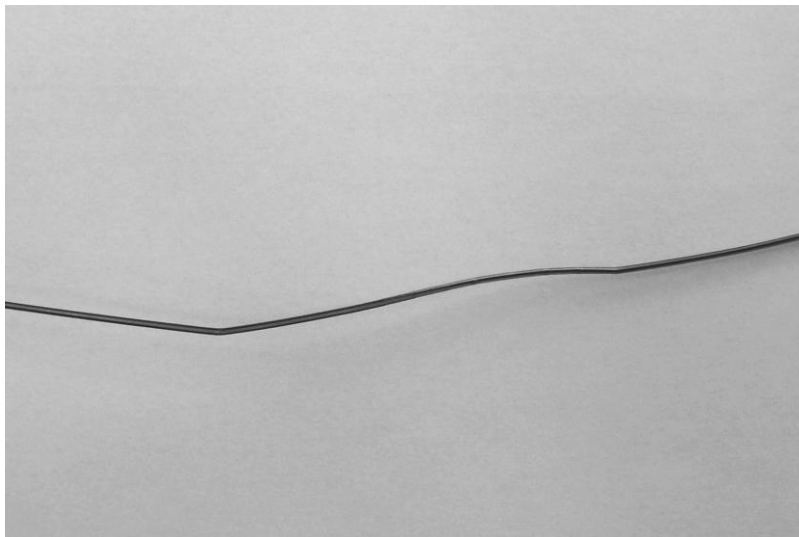
#### ***5.3.1.2 Testing method for resistance to breakage***

The coated guide wire was fixed to an assembly according to the DIN-norm. The guide wire was closely winded around a cylinder with a 10 times diameter of the guide wire. The testing assembly consisted of a cylinder with a diameter of 8 mm and a fixing unit with a gap of 9 mm to the cylinder. The diameters and the gap complied with the DIN-norm. Figure 5-3 shows the principle of the testing assembly, figure 5-4 shows a guide wire after the testing procedure.

The guide wire was clamped with the distal end at the fixing unit and winded with 8 completed closely windings around the cylinder. No breakage of the guidewires was detected and only a slight buckling/bending of the guide wire could be observed (Figure 5-4), thus fulfilling the DIN-norm.



**Figure 5-3. Assembly for breakage testing**



**Figure 5-4. Guide wire with buckling after the breakage testing**

### ***5.3.1.3 Testing method for tensile stress***

After the exposure of the test of bending and breakage the guide wires were tested for tensile stress. The guide wire was clamped to a weight of 2 kg and tested for tensile stress as shown in figure 5-5. The guide wire did not break under tension of 20 N.



Figure 5-5. Tensile test

This tensile test was repeated with the part, where the nitinol tip was glued to the rest of the guide wire (Figure 5-6). In this test the tensile stress on the wire was increased to 50 N. No breakage or damage on the fixation of the tip was noticed.





**Figure 5-6.** Tensile test of the fixing point between nitinol tip and guide wire

### **5.3.2 ASTM testing of the MR guidewire: RF safety, MR image artifacts and magnetic interaction**

The guide wire was tested by Philips Research Laboratories (Dr Sascha Krueger) to the following ASTM Standards:

1. ASTM F2182 - 02a: Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging
2. ASTM F2119 - 07 Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants
3. ASTM F2213 - 06 Standard Test Method for Measurement of Magnetically Induced Torque on Medical Devices in the Magnetic Resonance Environment

The RF-safety and magnetic interaction of the novel MR guidewire was used in a clinical 1.5T MRI scanner in comparison to a standard Nitinol reference guidewire.

#### **5.3.2.1 Material and Methods**

All tests were performed on a 1.5m long MR-guidewire as shown above and described in detail in the following: The MR guidewire features a base material with a diameter of less than or equal to 0.018'' (i.e.  $\leq 450\text{-}480\mu\text{m}$ ) of pultruded fiber-reinforced plastic material. The Nitinol (SE\_NT07\_SULOX\_0.400mm, @ Medical Technologies N.V., Herk-de-Stad, Belgium) tip section is 100mm long or shorter and shafted to the base (the diameter of the Nitinol part at the shaft is  $\leq 450\text{-}480\mu\text{m}$ , the diameter at the tip is approximately  $100\mu\text{m}$ ). For passive MRI visualisation, continuous and homogeneous Fe-doping of the wire matrix (1% of matrix mass) + additional discrete markers (steel wire pieces, length = 2mm, diameter =  $50\mu\text{m}$ ) every 100mm were used. A polymer jacket with biocompatible hydrophilic coating was used resulting in an outer diameter of at least 0.032'' (i.e. at least approximately  $800\text{-}820\mu\text{m}$ ).

The MR guidewire was examined for RF safety referring to ASTM F2182-02a inside a safety phantom described therein in a 1.5T clinical whole-body Philips Achieva MR system.

#### **5.3.2.2 Simulations**

Electromagnetic simulations using MoM (Method of Moments) analysis of FEKO (FEKO, Stellenbosch, ZA) were performed to estimate the device-induced local SAR for the 0.032'' MR guidewire in comparison with a typical 0.032 Nitinol-based guidewire which served as a reference (Terumo RF 32 GA, Terumo Corp., Tokyo, Japan). To this end, a realistic whole-body quadrature transmit coil at 64MHz (1.5T) was simulated. The devices were simulated by a cylindrical model containing an inner part (mainly GFRP and only 10cm of Nitinol for the MR guidewire and a full-length Nitinol core for the Nitinol-based reference guidewire) and a polymer sheath of appropriate thickness and diameter. The Nitinol wire was simulated to be in resonant condition. Practically, a wire of a resonant length of  $\sim 90\text{cm}$  was used in the simulations. In a realistic situation such a resonant condition is typically met at a certain insertion depth of 50-100cm depending on the electrical condition of the proximal part of the wire. The patient was simulated as a dielectric cylindrical lossy medium (dielectric constant  $\epsilon = 81$ , conductivity  $\sigma = 0.8\text{ S/m}$ ).

#### **5.3.2.3 RF safety**

Additional experimental safety tests were performed on an ASTM phantom (ASTM-2182.02). The details of the phantom were: Rectangular torso phantom morphology,  $>30\text{ kg}$  of tissue simulating phantom gel in basin, phantom gel composed according to ASTM

prescription (0.8 g/L NaCl + 5.85 g/L polyacrylic acid in distilled water (according to ASTM this results in a conductivity of  $\sim 0.8$  S/m @ 64MHz,  $\sim 0.4$  S/m @ 1kHz, Dielectric constant: 60-100 @ 64MHz, Diffusion constant:  $1.3 \cdot 10^{-7}$  m<sup>2</sup>/s, Heat capacity:  $\sim 4$ kJ/(kg\*K), high viscosity).

Temperature measurements were performed as follows: A 15 min laboratory temperature measurement (21  $\pm$  0.5) $^{\circ}$ C was performed. Subsequently, a 5 min phantom liquid measurement (21  $\pm$  0.5) $^{\circ}$ C was performed (phantom liquid was stored for >24h inside RF-cage). For the actual heating measurements, an MRI-Sequence: T1W-FFE, TR = 3.5ms, TE = 1.65ms, flip = 50 $^{\circ}$ , SAR = 3.9 W/kg (cf. also ASTM 2182-02a, section 8.6) was run on the scanner (the SAR calculation uses a patient weight of 30kg). This sequence has:  $B1_{rms} = 7.86\mu T$ ,  $1/TR = 286$  Hz,  $B1_{max} = 23.09\mu T$ .

A Luxtron 790 optical temperature probe (as recommended in ASTM 2182-02a) was positioned to be in contact with the tip of the guidewire, where the strongest RF heating can be expected. A reference probe was positioned inside the phantom fluid at a distance of >100mm from the metallic tip part of the guidewire (Figure 5-7).

The guidewire was placed at the largest possible off-isocenter position within the scanner bore. At large off center positions, higher electrical fields, and therefore, stronger RF heating are expected. Within the geometrical phantom boundaries, the positions of the positioning units were further optimized so that the Nitinol reference guidewire of the same length showed significant RF heating during the RF heating measurements as described below.

#### **5.3.2.4 MR image artifacts**

To obtain a realistic assessment of the image artifacts in-vivo, pig experiments were performed targeting e.g. renal and carotid arteries. Susceptibility-based image artifacts in MRI are strongly dependent on the MRI sequence and the local environment conditions such as e.g. blood flow, which effects convection of the dephased spins. Referring to ASTM F2119-01, the MRI image artifacts were investigated using the following typical interventional sequence: Cartesian balanced SSFP, TR = 4.2, TE = 2.1, slice thickness 5mm, Matrix 224x168, flip angle 35 $^{\circ}$ .

#### **5.3.2.5 Magnetic interaction**

The *magnetic torque* was assessed referring to ASTM F2213-04: For the determination of the magneto-static torque of the device ( $m=2$ g,  $l = 1.5$ m) an accuracy of  $1/10 \cdot g \cdot m \cdot l = 2.9 \cdot 10^{-3}$  Nm is required.

*Magnetically-induced displacement forces* were assessed referring to ASTM F20520-02.

### **5.3.3 Results and Conclusion**

#### ***5.3.3.1 Simulations***

The local guidewire-induced SAR for the MR guidewire, positioned for strong RF-coupling and therefore also RF heating, is a factor of 100 lower than for the Nitinol reference guidewire positioned identically. Of note is that this position may not even be the position of strongest RF heating for the Nitinol reference guidewire. To this end, the simulated SAR reduction yields a conservative estimation. There was an impression of significantly reduced local electrical fields for the MR guidewire compared to the reference guidewire.

#### ***5.3.3.2 RF safety***

The reference probe in the phantom showed no measurable temperature changes during the 5 min period prior to the RF heating measurements. The Nitinol reference guidewire was brought into a position of strong RF heating as described above using the mentioned positioning units. A temperature increase by almost 5K/(2W/kg) was measured. During execution of the MR sequence, for the MR-safe guidewire, a maximum temperature increase of only (0.1-0.2)K / 2W/kg) was measured at the device tip in the described phantom setup. Note that the measurement resolution of the Luxtron system is 0.1K. This demonstrated a significant local SAR reduction and reduction of RF heating to less than 1K/(2W/kg) of the MR guidewire compared to the Nitinol reference guidewire.

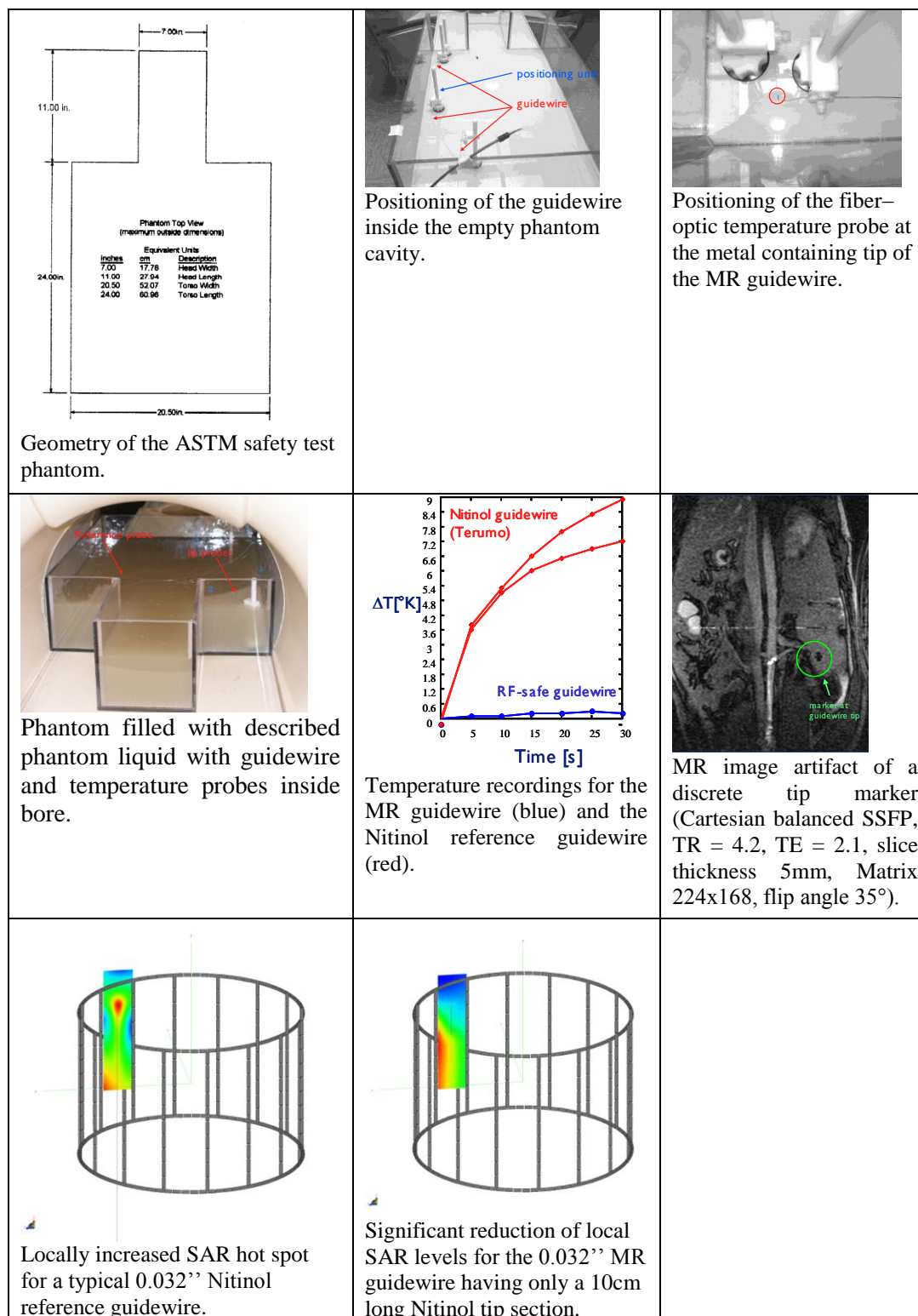
#### ***5.3.3.3 MR image artifacts***

Artifact size of tip in the described typical real-time balanced SSFP sequence used for interventional MRI procedures was 5-10mm.

#### ***5.3.3.4 Magnetic interaction***

Magnetic torque: No torque could be resolved within the given accuracy. Magneto-dynamic force was not applicable. Lorentz forces were not applicable as no currents were applied to the device.

Magnetically-induced displacement: No deflection could be resolved ( $\ll 5^\circ$ ). It could be concluded that the magnetically-induced forces were much lower than the weight of the device.



**Figure 5-7.** RF safety and magnetic interaction testing of the guidewire

### **5.3.4 Biological and Toxicological Safety of the guidewire coating**

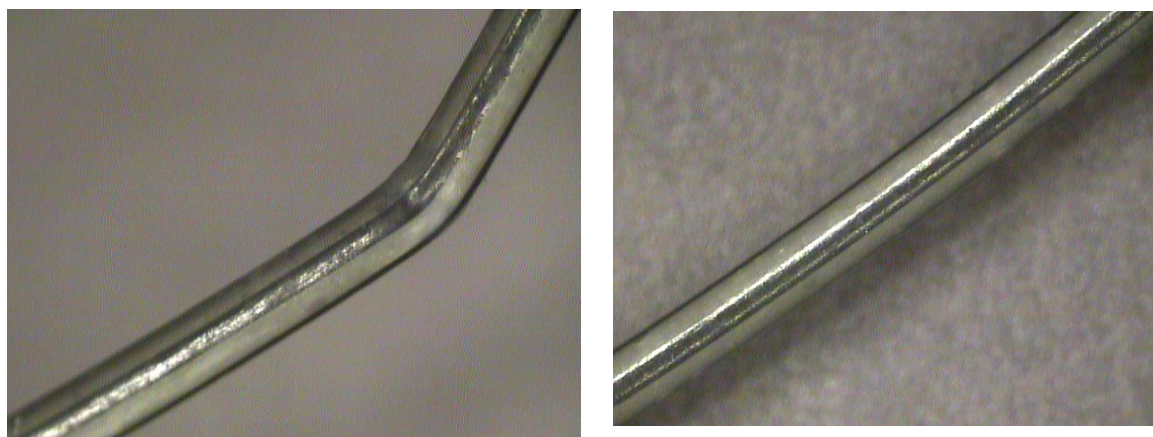
The guidewire was coated with Polyvinylpyrrolidone (PVP), type Kollidon 90F. PVP is widely used as excipient / additive in medicine, pharmaceuticals, cosmetics and foods. It has been used as plasma expander since the 1940s, and is metabolically inert in rat, dog and man as shown by experiments using  $^{14}\text{C}$ - or  $^{131}\text{I}$ -labelled PVP [Appendix].

The lubricious coating of the guidewires consists of PVP. The coating does not contain toxic additives. The solvents used for the coating procedure are non-toxic. After manufacturing, the coated guidewires are rinsed / incubated in pyrogen-free water 3 times (30 min each), dried in a sterile flow over night, with the consequence of complete volatilization of the used solvents. No peeling / flaking off could be observed after drying, indicating stability of the coating.

In summary, the biological / toxicological risks of the coating were regarded as very low. Even in the case of partial PVP abrasion during in vivo manipulation of the device, the risk would remain negligible due to the (documented) inertness of the coating.

### **5.3.5 Guidewire coating strength and flaking**

The surface of the guidewires has a smooth appearance. The coating itself is barely visible, due to its transparency. No flaking or scaling-off of the coating could be observed on the guidewire, especially at the bendings, which occurred after the breakage test (Figure 5-8).



**Figure 5-8. Guidewire coating strength and flaking assessment**

### **5.3.6 Wire sterilisation**

The guidewires were sterilised with Ethylene oxide. The sterilisation assessment proforma required by MHRA is given in Appendix.

### **5.3.7 Instructions for use**

The guidewire's instructions for use were produced prior to its use in the first-in-man clinical trial on MRI-guided interventions and are given the Appendix.

## **CHAPTER 6.**

### **MR-guided cardiac interventions using MR-compatible devices: Study protocol of the first-in-man clinical trial**

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Prior to starting the first-in-man clinical trial on MRI-guided interventions a study protocol was drawn up, which underwent Research and Development approval. The study protocol is outlined below:

#### **6.1 Background & Rationale**

Congenital heart defects are present in 6-8/1000 live births. For the majority of those the defect is minor, and either no treatment or a relatively straightforward procedure is all that is required. However, for a significant number of patients the cardiac defect is complex and requires surgical correction or transcatheter interventions through the major veins and arteries of the body or both. Up until now the transcatheter interventions have taken place in the catheterisation laboratory with the aid of fluoroscopy (X-Rays). This has two major drawbacks: a. poor visibility of the cardiac structures, as the interventions performed are based on angiograms taken following injection of contrast (dye) and b. the use of ionising radiation. Magnetic resonance imaging has become an increasingly important investigation in the diagnosis and management of congenital heart disease in recent years and has nearly completely replaced diagnostic cardiac catheterisations in institutions where it is available. Cardiac MRI is able to demonstrate with high-resolution the three-dimensional anatomy of complex cardiac abnormalities and in addition it is able to accurately determine the cardiac function and cardiac output. Moreover, when haemodynamic data (such as intracardiac pressures and oxygen saturations) are essential for the diagnosis and management of the patient, MRI-guided diagnostic cardiac catheterisations can be successfully performed, thus completely eliminating exposure to radiation.

The department of Paediatric Cardiology at Guy's and St Thomas' Hospital has been at the forefront of the development of cardiac MRI in children with congenital heart disease in the United Kingdom with an MRI program that dates back to the late 1990s. This program has increased to the point that as a unit we now perform in excess of 330 MRI scans and approximately 40 MRI-guided diagnostic cardiac catheterisations in children and adults with



congenital heart disease per year. Since 2002 a program also exists for performance of cardiac interventions using combined X-Ray and MR guidance (hybrid XMR interventions). The reason for having to use radiation up until now was the unavailability of an MRI compatible guide wire, which is essential to guide the cardiac catheters to certain places in or outside the heart and also provide a rail track for the interventional equipment (balloon catheters and balloon/stent assemblies) to travel on. Such an MRI compatible guidewire was recently developed, as described above, hence planning of the first in man study of completely MRI-guided congenital cardiac interventions took place. In addition to elimination of radiation exposure and improved visualisation of the target lesion, which can be of particular help in complex lesions with rotated anatomy, performance of the interventions under MR imaging would enable us to assess the end result by obtaining an MRI scan at the end of the procedure (ie: for quantification of valvar regurgitation following balloon dilation of a valvar lesion).

## **6.2 Trial Objectives, Design and Statistics**

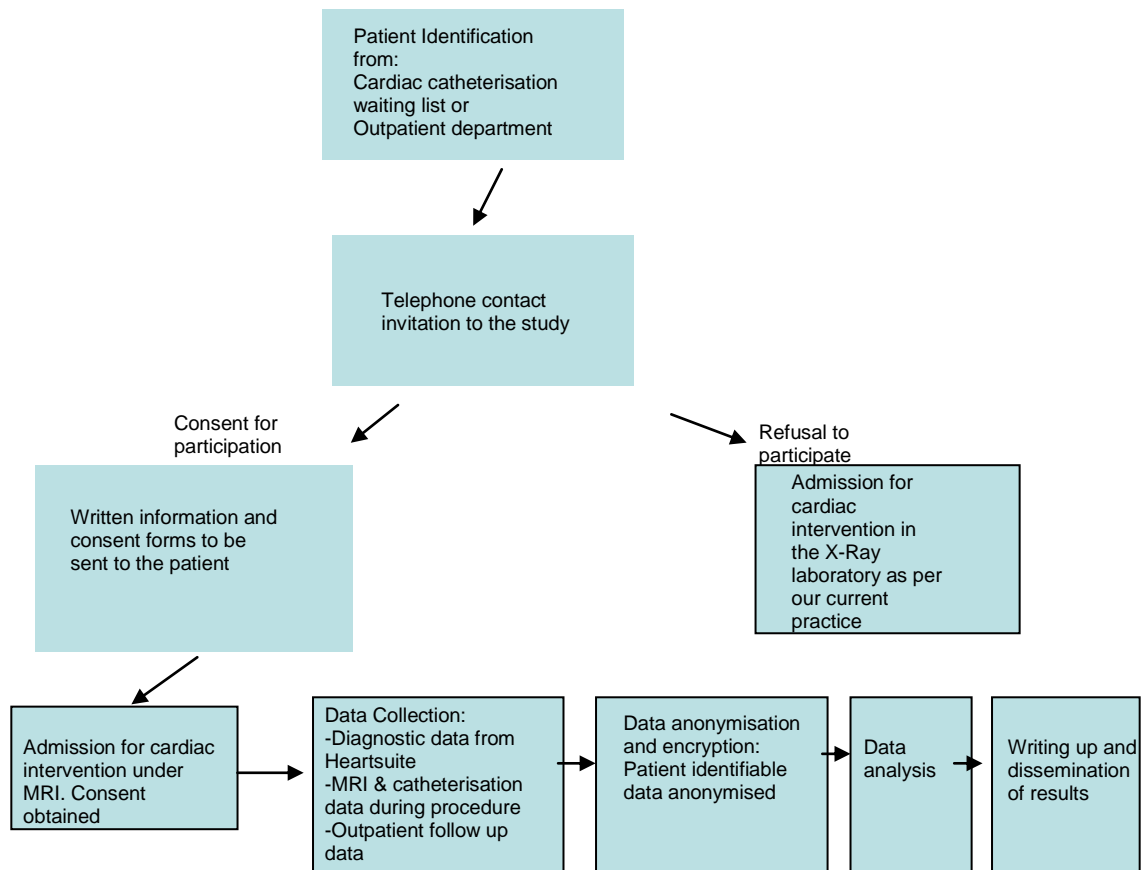
### **6.2.1 Trial Objectives**

The study's primary end point was to show the safety and efficacy of the MRI compatible guide wire, ie: to show that we would be able to perform the identical procedure to the X-Ray guided intervention without additional complications or adverse events related to the wire.

The secondary end point was the successful reduction of pressure gradient across the target stenosed lesion (>50%) for which the intervention was going to be performed

### **6.2.2 Trial Design & Flowchart**

This would be the first in man single arm interventional device trial. The study time scale was one year. Figures 6-1 and 6-2 give a schematic diagram of the trial stages.



**Figure 6-1.** First-in-man MR-guided interventions clinical trial flow chart

	Screen Visit	Day 1	Day 2-8
Patient identified and completion of Inclusion / Exclusion Criteria	X		
Patient information and informed consent	X		
Pre-catheter admission for patient work-up		X	
Interventional MRI- guided catheterisation			X
Patient follow-up			X

**Figure 6-2.** Trial Flowchart

### **6.2.3 Trial Statistics and Sample Size**

It was planned that twenty patients fulfilling the inclusion and exclusion criteria would be recruited. As this was going to be a feasibility study we looked at similar studies previously reported in the literature and the figure of approximately 20 patients had been used to demonstrate feasibility of new techniques to guide cardiac catheterisations.

### **6.2.4 Analysis**

This was going to be a non randomised trial In order to assess the primary outcome measures we planned to perform a descriptive analysis.

For the secondary outcome measures we were going to use age and procedure- matched historic controls and compare the percentage of success under the 2 methods. Interventional success would be defined as improvement in the degree of stenosis from pre- to post intervention of > 50% as measured by pull back pressure difference.

## **6.3 Selection and Withdrawal of Subjects**

### **6.3.1 Inclusion and exclusion Criteria**

It was decided to recruit patients above 2 years of age with specific cardiac lesions, such as valvar aortic and pulmonary stenosis, branch pulmonary artery stenosis and aortic coarctation. The age limit was set as such, because patients above 2 years of age were more likely to require balloon diameters above 14mm, which were compatible with 0.035 guidewires.

Inability to provide informed consent and contraindication to undertake an MRI scan (ie: because of pacemaker implantation, renal failure) would exclude patients from the trial. Patients would not be excluded on grounds of disability, gender, race, religion or belief or sexual orientation.

### **6.3.2 Withdrawal of Subjects**

Subjects would be withdrawn from the study if there was a change in their clinical status that rendered them unable to have an MRI scan (ie: pacemaker implantation, development of renal failure) or, if in the meantime, they or their guardian lost their ability to consent.

## **6.3 Assessment of Efficacy**

Assessment of the efficacy parameters would be performed by a. haemodynamic measurement of pressure gradients and b. performance of a brief MRI study to assess the degree of improvement across the target lesion and associated regurgitation (where applicable) and also by an echocardiogram, as routinely performed, to assess the interventional result. Primary efficacy parameter was set as the performance of the identical procedure to the X-Ray guided cardiac intervention without additional complications or adverse events related to the wire. Secondary efficacy parameter would be the reduction of pressure gradient across the target stenosed lesion for which the intervention was being performed by more than 50%.

## **6.5 Assessment of Safety**

### **6.5.1 Specification, Timing and Recording of Safety Parameters**

Before having an MRI scan all participants would be taken through the safety checklist by the researcher or clinician. This would preclude anyone with contra-indications to MR (e.g. pacemakers) from participating.

Unlike most medical imaging modalities, MRI does not use ionising radiation but instead generates images using magnetic fields and radio waves. MRI equipment is manufactured according to international safety standards (IEC 60601-2-33) to ensure that this imaging process does not have adverse effects on patients or volunteers. However, there are certain ‘indirect’ hazards, primarily the presence of a powerful magnet, which will exert strong forces on ferromagnetic objects brought close to the scanner. Rigorous safety policies are in place to minimise these risks, including local rules and training procedures that meet the requirements of the MHRA ‘Safety Guidelines for Magnetic Resonance Imaging Equipment in Clinical Use’ (2007 edition). MRI has been carried out on tens of thousands of patients and volunteers at Guy’s and St Thomas’ over a period of more than 20 years without a serious adverse incident. However, should an adverse events occurred, it would be recorded and monitored to ensure it would not lead to an adverse reaction.

### **6.5.2 Procedures for Recording and Reporting Adverse Events**

During study preparation we sought advice from expert staff working in the NHS Trust and the College. Approval of the device for the purpose proposed was sought and obtained from

the Head of Magnetic Resonance Imaging Physics of King's College London and a Senior Scientist from Medical Physics of Guy's and St Thomas' Hospital. A comprehensive and effective system was set in place for the reporting of any wire-related adverse incidents. This would be done in accordance with the MHRA bulletin no 3 on "Guidance on the operation of the EU vigilance system in the UK" and the MHRA device bulletin on reporting adverse incidents and disseminating medical device alerts.

## **6.6. Ethics & Regulatory Approvals**

The trial was set to be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and all of the applicable regulatory requirements. The Research and Ethics Committee to which the study protocol was submitted was the King's College Ethics Committee, which assesses regularly protocols relating to new medical devices (Appendix). In addition, an application was made to the UK Medicines and Healthcare Regulatory Authority (MHRA) for approval of the new medicinal device (MR compatible and safe fibreglass guidewire). Approval of the new medicinal device was granted by MHRA in November 2009 and the clinical trial was commenced a month later. In the following chapter, which is word for word our publication in *Circ Cardiovasc Intervent*, we describe in detail the performance of the pre-clinical animal trial and the two first-in-man MR-guided percutaneous cardiac interventions.

## CHAPTER 7.

### **MR-guided cardiac interventions using MR-safe passive devices: a preclinical study and first-in-man congenital interventions**

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#### **7.1 Introduction**

Diagnosis and treatment of patients with congenital heart disease has improved considerably over the past few decades, with more patients surviving into adulthood and more complex operations and interventions being performed across all age groups. Whilst echocardiography or MRI can easily assess cardiac anatomy and function, haemodynamic pressure measurements can only be performed invasively, mainly under X-Ray guidance. However, the use of radiation during repetitive X-Ray guided catheterisation has led to concerns relating to the risk of solid tumours in later life <sup>62,63</sup>, and that is particularly true in children in whom increased radiosensitivity, coupled with the possibility of repetitive exposure to diagnostic and interventional X-Ray procedures, can lead to a significant increase of cancer risk <sup>10-12</sup>.

In contrast, MR-guided *diagnostic* cardiac catheterisations involve no exposure to radiation and are currently established in some centers as their preferred method for assessment of pulmonary vascular resistance in children and adults <sup>2,22,64</sup>. As well as providing haemodynamic data, MRI-guided catheterisation procedures provide useful additional information, such as detailed delineation of the cardiac anatomy, flows across valves and in large vessels, pressure-volume loop relationships and ventricular function, leading to more accurate and informed treatment stratification and assessment of outcome. Furthermore, real-time visualisation of the cardiovascular structures in any required spatial orientation, and more detailed additional information obtained from 3D MRI scans, can be of particular benefit in patients with complex congenital heart disease.

Although, MR-guided diagnostic catheterisations are feasible without the use of a guidewire, catheter interventions nearly always require a suitable guidewire to aid and support the procedures. Standard guidewires, approved for X-Ray procedures, are manufactured from Nickel-Titanium superelastic memory alloys (Nitinol) or stainless steel. Due to the conductive properties of these materials and the length of the guidewire, radiofrequency (RF) coupling can cause significant heating of the material,<sup>37</sup> hence metallic guidewires are not applicable for MR-guided interventions in patients.

Continuous development of software and hardware has allowed the application of interventional MRI in animal models for many procedures currently performed under X-Ray guidance and for the in vivo monitoring of catheter-based vascular gene delivery <sup>65-67</sup>. However, some of the guidewires used in these studies, have not been proven to be RF safe,<sup>66</sup> whereas other RF safe polymer guidewires have not been found to conform mechanically to norms and do not provide adequate support for the interventional procedures <sup>67, 68</sup>. Overall, there have been no interventions in an animal model to date using a guidewire that is fully MR compatible and RF safe and has mechanical properties similar to the standard nitinol or stainless steel guidewires used in the X-Ray cardiac catheterisation laboratory. As a result, none of the above promising approaches for MRI-guided interventions had been translated so far into the clinical setting. An MR-safe guidewire with the mechanical features of a standard nitinol guidewire was developed and proposed recently <sup>61</sup>. This is the first guidewire that fulfils all prerequisites to become a clinical device with both actual safety proof and norm-conforming mechanical properties.

In the present study we report a. the pre-clinical assessment of the guidewire's behaviour when guiding and supporting MR-compatible catheters and valvuloplasty balloons for MR-guided interventions and b. the first-in-man MR-guided congenital cardiac interventions for two patients with pulmonary valve stenosis.

## **7.2 Methods**

### **7.2.1 Instruments**

#### ***7.2.1.1 Guide wire***

A non-metallic MR-compatible and safe guide wire (MR-GW) with features, properties and safety characteristics as described previously was used for all interventions <sup>61</sup>. The core of the MR-GW consists of an MR-safe glass fibre-compound and is produced using micro-pultrusion leading to a compound fibre with excellent flexural and torsional stiffness and improved kinking properties as compared to polyetheretherketon-based (PEEK) MR guide wires proposed previously <sup>68</sup>. A 10cm long cone-shaped Nitinol tip section is attached distally to provide superelasticity, higher flexibility and to allow shaping of the tip. The compound material is doped with iron at a concentration of 1% of the effective matrix mass to provide MR visibility over the full length. For accurate localisation of the tip, additional tiny iron splints of 50µm diameter and 2mm length are affixed along the distal 10 cm of the MR-GW

every 2cm, and then every 5cm for the next 30cm. A biocompatible hydrophilic coating (Lubriteq<sup>®</sup>, Hemoteq AG, Würselen, Germany) covers the jacket to reduce blood clotting and to ensure proper gliding within catheters and vessels. The diameter of the MR-GW is 0.032'' and comes in different lengths of 200 -300 cm.

#### **7.2.1.2 Catheters**

Balloon wedge pressure catheters (Arrow, Reading, PA, USA) were used for right and left heart catheterisation and to approach the target lesions. The balloon of the wedge catheter was filled with CO<sub>2</sub> and was passively visualised as a dark circular signal void in the bright blood pool on the SSFP images.<sup>69</sup> Commercially available, MR compatible valvuloplasty catheters (Tyshak II, NuMED, Hopkinton, NY) were used for balloon dilation of the great arterial valves, aortic arch and branch pulmonary arteries.

### **7.3. Pre-clinical animal study**

Five female domestic pigs were included, as approved by the government committee on animal experiments. All interventions were carried out under general anaesthesia at the University Hospital Aachen, Germany. The new MR-GW was used to aid balloon dilation of non-diseased pulmonary and aortic valves, aortic arch and branch pulmonary arteries. Each procedure was carried out twice in each animal and performed by two different operators out of a group of three experienced interventionalists (AT, GK and RR). Invasive pressure monitoring was not performed as there were no stenotic lesions and the main interest of the study was to assess the behaviour of the guidewire.

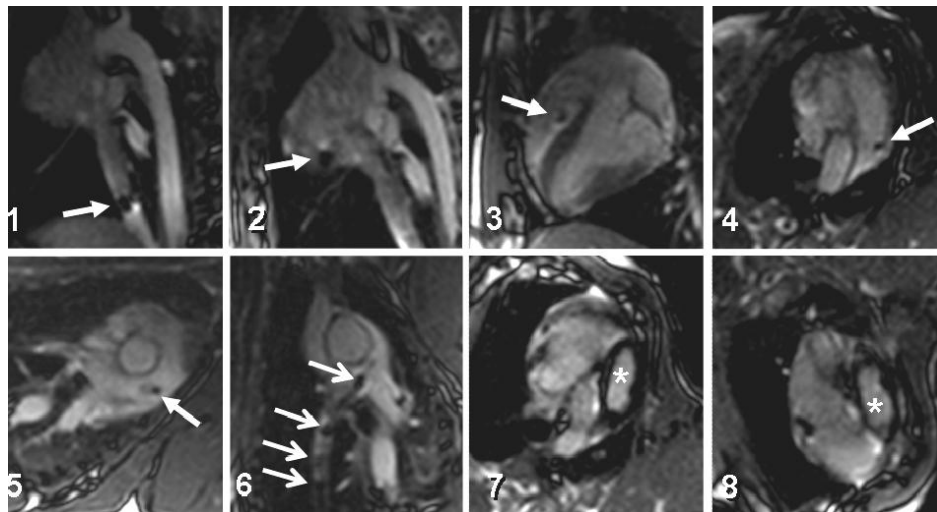
All interventions were performed on a clinical 1.5 T interventional MR system (Achieva, Philips, Best, Netherlands). Interactive real-time MR scanning was used to monitor the motion of the devices.

For right heart catheterisation the balloon wedge pressure catheter was advanced into the inferior vena cava and inflated with 1.25 ml of CO<sub>2</sub>, making it clearly visible as a dark signal void within the surrounding bright blood (Figure 7-1). The catheter was then advanced to the right ventricle (RV), main pulmonary artery (MPA) and right pulmonary artery (RPA) and the wire was introduced. The different spacing of the iron-splints on the wire allowed



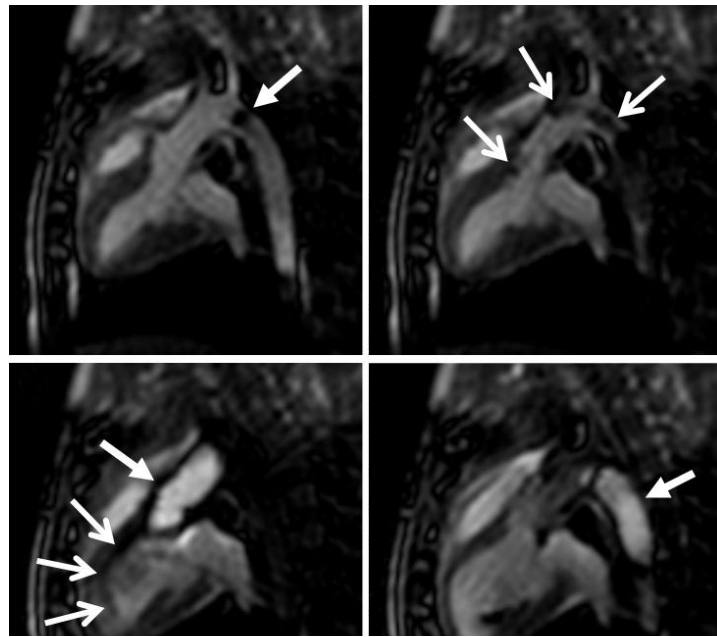
visual assessment of the wire length into the branch pulmonary artery (Figure 7-1). The balloon valvuloplasty catheter was introduced over the wire. In order to increase its visibility and facilitate correct positioning, 1 ml of Gd-DTPA (Magnevist, Beyer-Schering, Berlin, Germany) diluted in saline (1:10) was injected into the balloon. After placing it across the pulmonary valve, it was manually inflated up to 2 Atm and the pressure maintained for 5 seconds. With the wire in a stable position wedged into one of the pulmonary arteries, the valvuloplasty catheter was advanced into a branch pulmonary artery and balloon dilation was performed.

For left heart catheterisation the balloon wedge pressure catheter was first advanced into the descending aorta (Figure 7-2). The tip of the guidewire was shaped to a hook configuration and the guide wire advanced via the catheter into the aortic arch. Subsequently, the catheter and the guidewire were advanced into the ascending aorta and the aortic valve was crossed. The balloon valvuloplasty catheter was manually inflated with diluted Gd-DTPA at a sustained pressure for 5 seconds. With the wire in a stable position in the left ventricle, the valvuloplasty balloon was withdrawn to a level distal to the left subclavian artery and balloon dilation of the aortic arch was performed (Figure 7-2).



**Figure 7-1.**

Dilation of a pulmonary valve in a swine. The images show the CO<sub>2</sub> filled wedge catheter as a dark spot in the inferior vena cava (1), the right atrium (2), the right ventricle (3) and the main pulmonary artery (4,5). The guidewire was inserted into the catheter and advanced into the right pulmonary artery (6). Note that the in-between distance of the inferior 3 arrows represents the 2 cm distance between the iron oxide markers. The balloon wedge catheter was exchanged for the valvuloplasty catheter and advanced to the pulmonary valve. The balloon was inflated with diluted Gd-DTPA (7 and 8 asterisk) and the pulmonary valve was dilated.



**Figure 7-2.**

Dilatation of the aortic valve and arch in the swine. The CO<sub>2</sub> filled wedge catheter is seen in the descending aorta (1), with the wire advanced into the ascending aorta (2, open arrows: guidewire) and into the left ventricle. The valvuloplasty catheter is inflated across the aortic valve (3) and distal to the left subclavian artery (4).

## 7.4 Clinical first-in-man congenital cardiac interventions

Ethical approval for the performance of MRI-guided interventions for adults and children with congenital heart disease was obtained by an expert UK based device research ethics committee. Inclusion criteria for patient participation in the clinical trial were: simple congenital intervention, such as pulmonary or aortic valvuloplasty, ballooning of branch pulmonary artery or aortic arch or pre-implanted stents in the above positions, and age > 2 years old. The new MR-GW was assessed and approved by the UK Medicines and Healthcare Products Regulatory Agency (MHRA). The first-in-man procedures were performed at the Evelina Children's Hospital, St Thomas' Hospital, London, UK. The procedures were performed under general anaesthesia, as per our routine practice for such congenital cardiac interventions in our hospital.

Two patients with pulmonary valve stenosis underwent MR-guided balloon dilation of their pulmonary valves. The first patient was a 6-year-old boy, who had progression of valvar pulmonary stenosis (PS) with peak echocardiographic gradient of 63 mmHg. Following informed consent the parents opted for the MR-guided interventional study. The second

patient was a 43-year old man with valvar and subvalvar pulmonary stenosis and severe right ventricular hypertrophy. Doppler Echocardiography revealed double envelope, indicating both valvar and subvalvar pulmonary stenosis and a peak gradient of 110mmHg. Both patients had an intact septum, were fully saturated and were clinically asymptomatic.

The procedures were performed on an interventional 1.5T MR-scanner (Achieva, Philips, Best, Netherlands) in our combined X-Ray/MRI laboratory with the X-Ray equipment readily available for emergency bailout if required. We used the commercially available haemodynamic monitoring system EP Tracer 102 (CardioTek B.V, Maastricht, Holland) for haemodynamic pressure monitoring. The haemodynamic traces were displayed on one of the 2 panels in the mini in-room console, with the other panel displaying the i-MRI sequences. The operator could start and stop the interactive scanning independently using foot pedals, which also facilitated the adjustment of the imaging plane and slice position in order to get the interventional devices in view.

Cannulation of the femoral vessels was performed at the beginning of the procedure and the patient was moved into the MRI scanner. For both patients the same scan protocol with similar scan parameters were used (Table 5-1), except for a higher spatial resolution used in the paediatric case. Following a plan-scan and sense reference scan, 2D SSFP cine MRI sequences were performed to assess the valve lesion. An ECG-triggered, free-breathing 3D SSFP scan and 2D quantitative phase contrast flow scans (Table 7-1) were used to measure the lesion size and maximum flow velocity through the lesion.

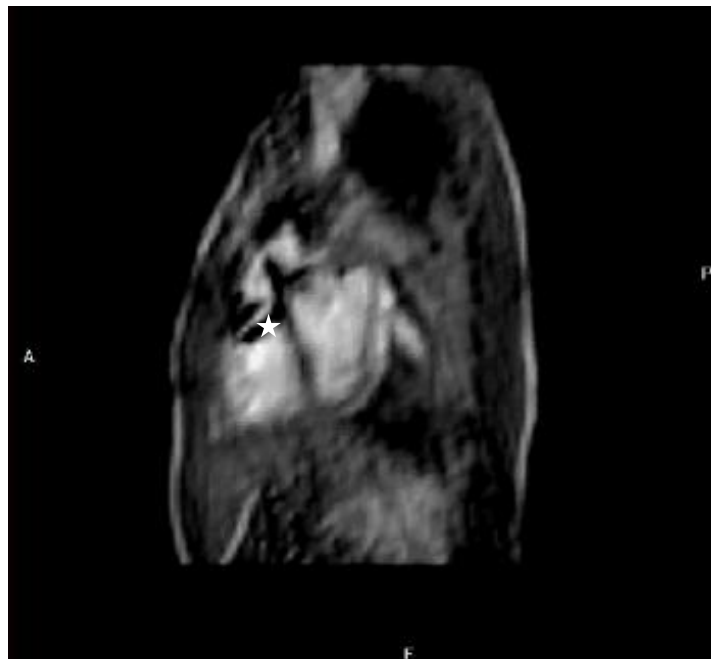
The common imaging planes for catheter guidance were identified and stored. Balloon visualisation was facilitated with injection of Endorem 5% (for the adult patient) and dilute Gadolinium 1:10 (for the paediatric patient) into the balloon lumen. Cine and phase contrast flow images were repeated after the intervention, to assess the haemodynamic result.

## 7.5 Results

**Clinical case 1 (Paediatric):** MRI assessment of the pulmonary valve revealed bicuspid pulmonary valve (BPV) with diameter of 22x22mm and effective orifice area of 49mm<sup>2</sup>. A 6Fr wedge catheter was used for right heart catheterisation and to cross the pulmonary valve. Baseline haemodynamic gradient between the RV and MPA was 44mmHg. The wedge catheter was advanced to the distal LPA and the MR wire was introduced through the catheter to the distal vasculature and visualised on the sagittal view with the iron splints easily visible.

We observed no artifacts caused by the iron markers on the wire. A 22mm Tyshak balloon was initially used and inflated for 5sec. The waist seen on it was completely abolished (Figure 7-3). Repeat pressure measurement revealed mild gradient improvement to 30mmHg, hence a 25mm Tyshak II balloon was inflated across the valve as previously. Repeat gradient assessment showed further improvement to 25mmHg. No further attempts on inflating the pulmonary valve with a bigger balloon were made, due to the bicuspid nature of the valve and the fact that balloons bigger than 25mm would be inappropriately big for a child of this age. Repeat cine MRI assessment revealed increase of the effective orifice area on of the pulmonary valve from 49 to 92mm<sup>2</sup>. Phase contrast flow images showed no valvar regurgitation before and mild valvar regurgitation after the procedure (regurgitant fraction of 7%). The total catheterisation time was 110min and total procedure time with the pre- and post-procedure MRI was 200min.

The procedure was well tolerated by the patient who was woken up immediately after and was transferred to the cardiac ward 30 min later. Peak echocardiographic gradient as assessed the following morning had improved from 63mmHg prior to the procedure to 22mmHg after the procedure and the patient was discharged home a few hours later uneventfully.

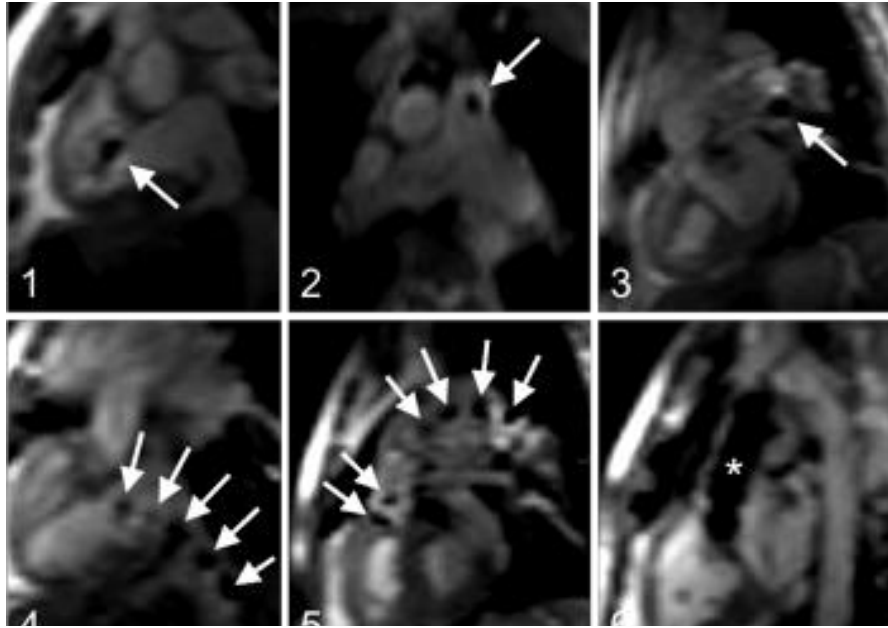


**Figure 7-3.**

Dilatation of the pulmonary valve in a paediatric patient. The valvuloplasty balloon (asterisk) was inflated with diluted Gd-DTPA and the pulmonary valve was dilated.

**Clinical case 2 (Adult):** The patient had known valvar and subvalvar pulmonary stenosis, hence it was decided to alleviate the valvar component and reassess the subvalvar gradient at later stage. MRI assessment of the pulmonary valve revealed valve diameter of 21x24mm. In-plane phase contrast flow images showed maximum velocity across the pulmonary valve and the sub-valvar lesion of 3.1m/s and 2.3m/s, respectively. A 6Fr wedge catheter was used. The catheter was advanced into the LPA and then in the LPA wedge position. The MR compatible guidewire was advanced through it and its position was confirmed on the LPA sagittal view, where the iron markers were easily visible. The catheter was then withdrawn and a 23mm Tyshak II balloon was advanced over it. Visualisation of the balloon was achieved with injection of 1ml of 5% Endorem in the balloon lumen. After correct positioning was confirmed, a full inflation was performed on the sagittal RVOT view (Figure 7-4). Repeat pressure measurement did not reveal significant haemodynamic improvement, hence a 25mm Tyshak balloon was chosen and inflated across the pulmonary valve. RV pressure at the end of the procedure remained systemic due to infundibular collapse, as evidenced on the haemodynamic trace and the phase contrast flow images. Velocity across the valve and sub-valvar lesion was 2.5m/s and 2.6m/s, respectively. Gradual pullback from the MPA to beneath the pulmonary valve and then to the RV revealed a gradient of 17mmHg across the pulmonary valve and 60mmHg across the infundibular stenosis, confirming our initial suspicions that a significant subvalvar component was going to be present at the end of the procedure. The total catheterisation time was 80min and total procedure time with the pre- and post-procedure MRI was 170min.

Peak echocardiographic gradient prior to the procedure was 110mmHg with double envelope trace (indicating valvar and subvalvar stenosis), which improved to 70mmHg after the procedure with change of the Doppler pattern from double to single envelope. The patient was commenced on b-blockade with propranolol, in an attempt to induce infundibular relaxation, until such time that the RV hypertrophy regressed sufficiently as a response to the valvar stenosis relief. No complications were noted and he was discharged home the following day. Repeat echocardiography 2 months after the procedure revealed further RVOT gradient reduction to 45mmHg.



**Figure 7-4.**

Dilatation of the pulmonary valve in an adult patient. The CO<sub>2</sub> filled wedge catheter appears as a dark spot in the right ventricle, (1) main pulmonary artery (2) and the left pulmonary artery on the sagittal view (3). The course of the guidewire with its iron markers is seen on the sagittal view of the IVC/RA junction (4) and from the RV into the left pulmonary artery (5). The valvuloplasty balloon was inflated with 5% Endorem (6 asterisk) and the pulmonary valve was dilated.

## 7.6 Discussion

Since 2001 there have been a number of animal studies showing the safety and efficacy of interventional MRI for a multitude of procedures that are currently performed under X-Ray guidance.

In particular, animal interventional MRI has been used to facilitate procedures such as creation or closure of atrial septal communications<sup>44-47</sup>, intracoronary imaging<sup>48</sup> as well as coronary and carotid artery interventions<sup>49-53</sup>, stenting of pulmonary arteries<sup>54</sup>, aortic coarctation<sup>55,56</sup>, and vena cava interventions<sup>57,58</sup>. The procedures have been aided by the use of non MR-safe active guidewires and prototype or commercially available devices and were either solely MR-guided or combined with conventional catheterisation before and after the procedure.

Active guidewires are tracked or visualised by employing miniature RF-coils or loopless antenna both connected to the scanner using a long metallic wire. This long wire can

heat up to 70°C due to resonating RF waves<sup>37</sup>. New strategies for safe active devices have been proposed including optical transmission and use of transformers to shorten the length of the conducting wire,<sup>38,39</sup> however no safe active guidewires have been developed so far. Semi-active catheters use tuned fiducial markers that produce increase MR signal locally without wires connecting to the scanner.<sup>40</sup> There are however issues with miniaturisation and the ability of firmly securing these markers to catheters. Passive guide wires have the advantage of no risk of heating, but the disadvantage of being less visible than active guide wires and requiring manual tracking and changing of the imaging plane to keep the wire in view.

MRI guided cardiac interventions have also been performed without the use of a guidewire, in an animal model for transcatheter implantation of a prosthetic valve in the aortic valve position<sup>59</sup>, and in patients who underwent balloon dilation of aortic coarctation, using a self-made non-metallic guidewire that was advanced just up to the distal port of the balloon catheter<sup>60</sup>.

Translation of the animal MR-guided interventions in humans had not been made possible to date due to the lack of fully MR compatible equipment. Recently an MR-safe guidewire fulfilling all prerequisites to become a clinical device has been developed. As a pre-clinical step, we used this guidewire in combination with already available MRI safe catheters to perform solely MR guided cardiac interventions in an animal model and then performed the two first-in-man congenital cardiac interventions. The interactive scanning parameters were optimised to improve temporal resolution to 11-12 frames/sec (Table 7-1). Similar frame rates are used for X-Ray fluoroscopy in other institutions, particularly in longer procedures as a way of reducing X-Ray radiation dose. We used an 8-10mm thick imaging slice, hence the iron oxide markers within that slice were easily visualised. For the part of the wire outside that imaging slice we manually moved left and right of the current imaging slice by using the foot pedals, while the wire position was kept constant. During manipulation of catheters and balloons over the wire a key-imaging slice, which showed most of its length was imaged in real time with particular attention being paid to the iron oxide marker to ensure wire stability. During the balloon dilation we could visualise the valve and subvalvar area as well as the pulmonary artery, while under X-Ray we would only see the balloon, hence structural visualisation was much superior compared to X-Ray.

Our first patient had a bicuspid pulmonary valve, a very rare congenital entity encountered in only 0.05-0.1% of the population<sup>70-72</sup>. Although complete abolition of the balloon waist was achieved, there was still some residual pulmonary stenosis gradient at the end of the procedure, which was attributed to the bicuspid nature of the valve. The patient's

haemodynamic gradient was reduced by 43% and his peak echocardiographic gradient by > 60%. Our second patient was complicated by dual pathology with valvar and subvalvar pulmonary stenosis. Haemodynamic and MRI assessment at the end of the MR-catheterisation procedure revealed that the valvar gradient was now negligible. The RVOT gradient decreased by 60% on echocardiogram. In both patients we deliberately undersized the balloon, which should have been 120-150% of the pulmonary valve annulus, due to the interventions being the first two in the trial, hence a more conservative approach was followed. The contrast material used to facilitate better visualisation of the valvuloplasty balloon differed between the paediatric and the adult case. This was due to the fact that the iron oxide agent Endorem, which would have been our preferred choice across all ages due to its superior visualisation properties, is not currently licenced for children and we would only use it in patients > 18 years of age. Endorem is used in adults for MR imaging of the liver. The intravascular dose used in these patients is 0.075ml/kg of the 0.2mmol/ml concentration. If Endorem was to be used for liver imaging in our adult patient who weighed 60kg, the recommended dose would have been 4.5mls. We used an Endorem concentration of 5%, and the absolute dose of 1 ml, hence even if the balloon burst, the total dose of endorem that would reach the circulation would have been well below the dose that is used in clinical practice.

We have been encouraged by the successful outcome of our first two clinical cases, but we need to evaluate the feasibility, safety and efficacy of the MR-guided interventions further. To this end, a clinical trial on MR-guided cardiac interventions for commonly encountered lesions, such as aortic and pulmonary valve stenosis, branch pulmonary artery or aortic arch stenosis or dilatation of stents previously implanted in those vessels is ongoing. A committee has been set up to assess the safety and clinical outcome of the interventions. We hope that in the future MR-guided interventions will replace some cardiac catheterisation procedures performed in patients with congenital heart disease. The option of performing such interventions in the MRI suite is particularly appealing due to the lack of radiation, additional physiological data obtained and soft tissue characterisation. The latter is of particular relevance in interventional procedures, as real time i-MRI is hoped to offer early recognition and response to complications such as vascular rupture<sup>56</sup> or impending cardiac tamponade<sup>73</sup>, though clinically this is yet to be proven.



## **7.7 Limitations**

The study is small but a clinical trial is underway. The catheterisation procedure times were long and the performance of an MRI before and after the intervention has added significantly to that time. We hope that the procedure time will shorten after our initial learning curve. The spatial and temporal resolution was acceptable to the operators in this study but we are working on further improving it for future interventions.

In conclusion, we have demonstrated the feasibility of MRI-guided cardiac interventions using an MR-compatible guidewire. Future study is needed to determine whether the outcomes for MR-guided procedures are comparable to those guided by fluoroscopy.

**Table 7-1. MR-scan parameters of the patient scans for the assessment of function, anatomy, angiography, flows and intervention**

Scan Type	Patient 1 (6 years)	Patient 2 (42 years)
Function - 2D/M2D Cine	Res.: 1.7x1.7x8 mm <sup>3</sup> SENSE = 2 SSFP-contrast TR/TE = 3.2/1.6ms Flip-angle = 60 Heart phases 60 Breathhold 14s	Res.: 2.2x2.2x10 mm <sup>3</sup> SENSE = 2 SSFP-contrast TR/TE = 3.0/1.5ms Flip-angle = 60 Heart phases 40 Breathhold 15s
Anatomy – 3D whole heart	Res.: 1.3x1.3x1.3 mm <sup>3</sup> SENSE = 2 SSFP-contrast TR/TE = 4.9/2.4ms Flip-angle = 90 T2-prep TE=35ms TFE-factor=20 ECG trigger: diastole Free-breathing, resp. gating window= 3mm Scan time 3min (100% efficiency)	Res.: 1.6x1.6x1.6 mm <sup>3</sup> SENSE = 2 SSFP-contrast TR/TE = 4.7/2.3ms Flip-angle = 90 T2-prep TE=35ms TFE-factor=28 ECG trigger: diastole Free-breathing, resp. gating window= 3mm Scan time 3.4min (100% efficiency)
Angiography – 3D MRA	Res.: 1.8x1.8x1.8 mm <sup>3</sup> SENSE=2 T1-contrast TR/TE = 4.1/1.3ms Flip-angle = 40 Single breathhold	Res.: 2.2x2.2x2.2 mm <sup>3</sup> SENSE=2 T1-contrast TR/TE = 3.5/1.1ms Flip-angle = 40 Single breathhold
Flows – In/through-plane 2D-PCA	Res.: 1.6x1.6x6 mm <sup>3</sup> SENSE=2 T1-contrast TR/TE = 4.7/ 2.9 Flip-angle = 15 VENC=350cm/s	Res.: 2.2x2.7x6mm <sup>3</sup> SENSE = 2 T1-contrast TR/TE = 4.3/2.6 Flip-angle = 15 VENC=380cm/s
Intervention - real-time interactive	Res.: 2.2x2.2x8 mm <sup>3</sup> SENSE=1.5 SSFP-contrast TR/TE = 2.5/1.1ms Partial Echo Half-scan=0.62 Flip-angle = 45 Temp. Res: 11 frames/s	a)Res.: 2.5x2.5x10 mm <sup>3</sup> SENSE=1.5 SSFP-contrast TR/TE = 2.4/1.0ms Partial Echo Half-scan=0.62 Flip-angle = 45 Temp. Res: 12 frames/s  b)Res.: 4x5x8 mm <sup>3</sup> SSFP-contrast TR/TE = 2.6/1.3ms Flip-angle = 45 Temp. Res: 7 frames /s

## CHAPTER 8.

### **Results of the first-in-man MRI guided cardiac interventions.**

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#### **8.1 Abstract**

In total, seven patients aged 3 - 64 years were recruited in the clinical trial. Five patients underwent successful interventions for pulmonary valve stenosis (n=4) and native aortic coarctation (n=1). One patient with left pulmonary artery stent underwent right heart catheterisation with the aid of the new MR-wire, but the gradient across the stent was minimal, hence no intervention was required. The last patient (8 year old child) with severe aortic stenosis had an unsuccessful attempt at balloon dilation of the aortic valve, due to the inability of turning the wedge catheter into the ascending aorta, as the balloon of the catheter kept being pushed back by the aortic stenosis jet. This patient was then referred for X-Ray guided balloon dilation of the aortic valve.

Catheter manipulations were monitored with real time MRI sequence with interactive modification of imaging plane and slice position. Temporal resolution was 11-12 frames/sec. Median procedure and catheterisation times were 180 and 110 min, respectively. All patients, except for the last, were discharged home the day after the procedure with > 50% reduction of the stenosis gradient and no procedural complications.

#### **8.2 Details of further patients enrolled in the clinical trial**

The first two patients enrolled in the clinical trial are described in Chapter 7. We hereby provide the clinical and procedural data of the remaining patients in the trial.

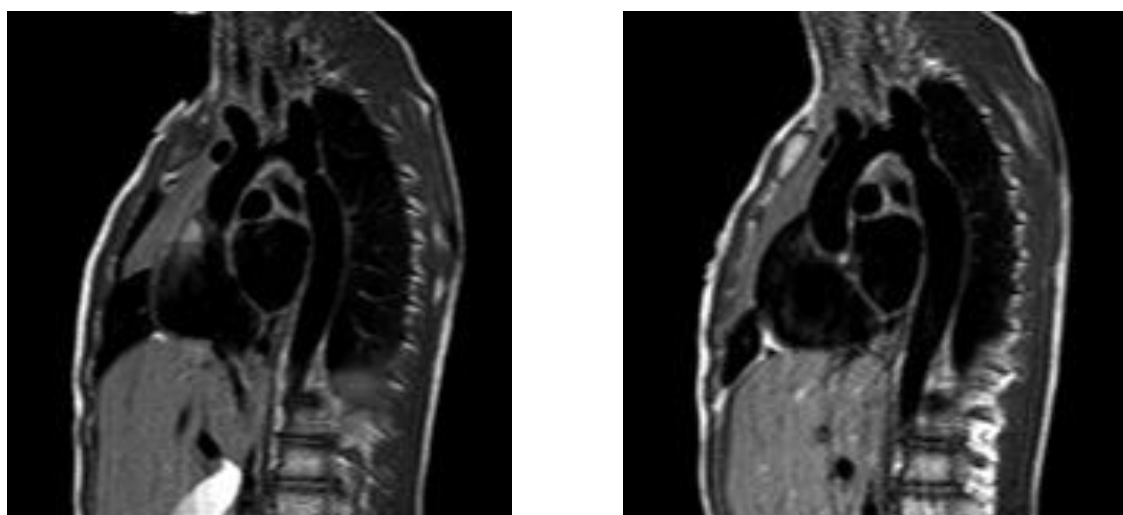
**Clinical case 3:** A five-year-old patient with an antenatal diagnosis of possible coarctation was followed up for progressive aortic arch stenosis. The gradient across the stenotic isthmus had increased to 60mmHg over time and therefore she was listed for a transcatheter intervention. Through a 7Fr sheath a 6Fr wedge catheter was inserted and advanced above the CoA. The position of the catheter was tracked by keeping the balloon at its tip inflated. Once the catheter was above the CoA, its tip was attempted to turn into the ascending aorta but this

proved unsuccessful, even when the wire was used to guide it. Eventually, the MR guide-wire was positioned in the left subclavian artery and its location was confirmed on the coronal plane under real-time interactive MRI. The arch measurements were assessed using black blood imaging. The transverse arch measured 12mm, the area above and below the CoA 14mm and the descending aorta 12mm. The isthmus appeared tight with a diameter of 3-4mm.

With the wire in good position in the left subclavian artery, the wedge catheter was withdrawn and a 14mm Tyshak II balloon was advanced over it. Visualisation of the balloon was achieved with injection of 1ml of 5% Endorem in the balloon lumen. After correct positioning was confirmed, a full inflation was performed on the sagittal plane. A waist was clearly seen, which was abolished completely. The stenotic area at the isthmus improved from a diameter of 3-4mm to 9mm (Figure 8-1). Repeat MRI after the intervention revealed a tiny flap at the ductal aspect.

The total catheterisation time was 40min and total procedure time with the pre- and post-procedure MRI was 110min.

Peak echocardiographic gradient prior to the procedure was 60mmHg, which improved to 30mmHg after the procedure and 20mmHg at follow-up 18months later. No complications were noted and the patient was discharged home the following day. He remains well 2 years after the procedure.



**Figure 8-1.**

Black blood imaging showing the coarctation at the isthmal area. On the right hand panel repeat black blood imaging after balloon dilation of the CoA reveals normal arch anatomy with no residual coarctation

**Clinical case 4:** A 65 year old patient with known valvar pulmonary stenosis, after pulmonary valvotomy at the age of 6 years underwent an MRI scan 2 months prior to the MRI-guided catheterisation, which showed extremely dilated LPA and vascular tree, possibly consistent with pulmonary hypertension in the left lung. She also had valvar pulmonary stenosis with borderline gradient of 38mmHg. It was decided to catheterise her, assess the pulmonary artery pressures and resistance and perform an MR-guided balloon valvuloplasty, if clinically appropriate. Under MR interactive scanning, the wedge catheter was advanced through a short groin sheath to the RA and RV. Isoprel was given for gradient assessment. The RV pressure was found to be suprasystemic at stress. The wedge catheter was then advanced to the MPA and LPA. The LPA pressure and left lung PVR were normal. The MR-compatible wire was then introduced and wedged distally in the LPA. The wedge catheter was exchanged for a 25mm Tyshak II balloon. Visualisation of the balloon was achieved with injection of 1ml of 5% Endorem in the balloon lumen. After correct positioning was confirmed, a full inflation was performed on the sagittal RVOT view.

Two inflations did not seem to produce any waist. Repeat gradient assessment revealed no pressure difference. Given that the valve had measured about 24mm both on echocardiogram and MRI assessment, the valvuloplasty balloon was upsized to 30mm and inflated across the valve. Repeat gradient assessment with and without isoprenaline confirmed good result with pullback gradient between MPA and RV of 20mmHg. The total catheterisation time was 120min and total procedure time with the pre- and post-procedure MRI was 230min.

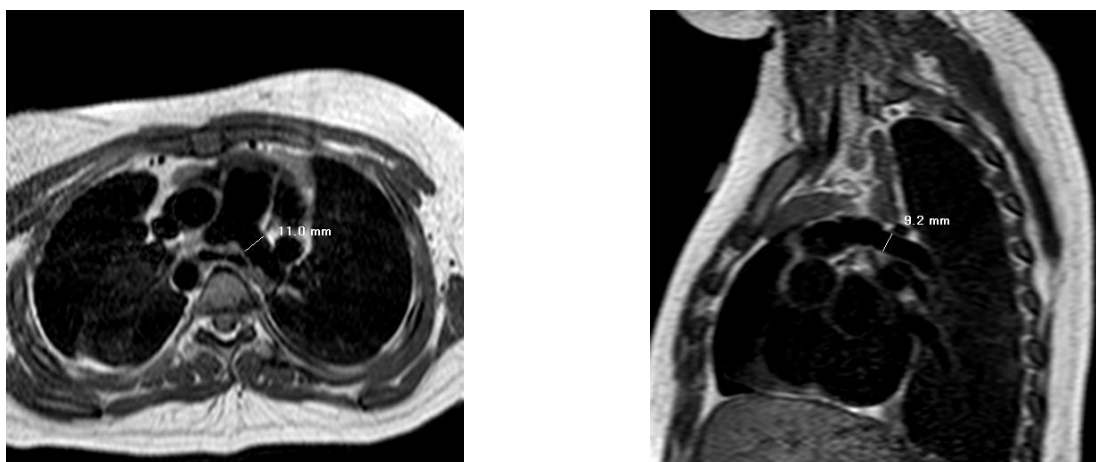
No complications were encountered and the patient was discharged home the following day. Echocardiogram at discharge showed an eccentric RVOT jet with gradient of 24mmHg.

**Clinical case 5:** A 3.5yr old boy with tetralogy of Fallot and bicuspid PV was diagnosed with significant valvar pulmonary stenosis 2.5 years after Fallot repair and concurrent anterior commisurotomy intraoperatively. He was well clinically, but was noted to have an increasing gradient across the pulmonary valve of 66mmHg.

During the MR-guided procedure, a wedge catheter was advanced to the right atrium, right ventricle and right pulmonary artery. The gradient across the pulmonary valve was 30mmHg. Based on echocardiographic and MRI measurements, the pulmonary valve was dilated with a 14mm Tyshak II, but this did not reduce the gradient, which was remeasured to be 29mmHg. The balloon was upsized to a 16mm Tyshak II and the valve was re-ballooned. A balloon waist was clearly seen on interactive MRI, which was completely abolished. Repeat

pressure measurements showed a transvalvar gradient of 18mmHg. In order to assess the residual gradient at stress 2mcg of isoprenaline were given. The right ventricular pressure only rose to 2/3 systemic and hence the procedure was terminated. The total catheterisation time was 120min and total procedure time with the pre- and post-procedure MRI was 220min. No complications were noted. The patient remains well 2 years after the procedure with laminar flow into the pulmonary artery and minimal pulmonary regurgitation.

**Clinical case 6:** An eleven-year-old girl with unoperated partial AVSD and previous LPA stenosis, which had been stented at the age of 1 year, was scheduled for cardiac catheterisation prior to surgical repair and balloon dilation of the stent if it was found stenosed during catheterisation. MRI just prior to the MR-guided catheterisation showed good-sized branch pulmonary arteries of the same diameter, approximately 10mm. The LPA stent appeared patent on the black blood images (Figure 8-2). Differential flows between the two lungs showed flow to the right lung of 59% and left lung 41%. With a wedge catheter the pressures in the right ventricle and the branch pulmonary arteries were obtained. An attempt was made to cross the LPA stent with the wedge catheter, but it was not successful, hence the stent was crossed with the aid of the MR-compatible wire. Equal pressure gradient across the distal pulmonary arteries and the MPA was obtained of approximately 20mmHg. The overall Qp:Qs was 1.5:1. The pulmonary vascular resistance was moderately raised at  $3.9\text{WU.m}^2$  with the left and right lung PVR being  $7.5\text{WU.m}^2$  and  $5\text{WU.m}^2$ , respectively. No intimal proliferation was noted inside the stent and hence no intervention was performed. The total catheterisation time was 40min and total procedure time with the pre- and post-procedure MRI was 180min. The patient proceeded with subsequent corrective surgery successfully.



**Figure 8-2.** Black blood imaging shows patent LPA stent both on the axial and sagittal views

**Clinical case 7:** The last patient enrolled in the clinical trial was an eight-year girl with VSD and arch hypoplasia, which had been repaired at the age of 1 month. She also had aortic stenosis due to bicuspid aortic valve, the severity of which had progressed significantly over the past few years. When the gradient across the aortic valve increased to 60mmHg she was listed for a transcatheter intervention.

Through a 7Fr sheath a 6Fr wedge catheter was inserted and advanced to the level of the left subclavian artery. With the aid of the wire, the catheter was attempted to turn into the ascending aorta but without success as the balloon of the catheter kept being pushed back by the aortic stenosis jet. To this end, it was decided to exchange the short sheath for a long Mullins sheath, which would be placed in the ascending aorta in order to provide stability for the wedge catheter and better alignment for the guidewire to cross the valve.

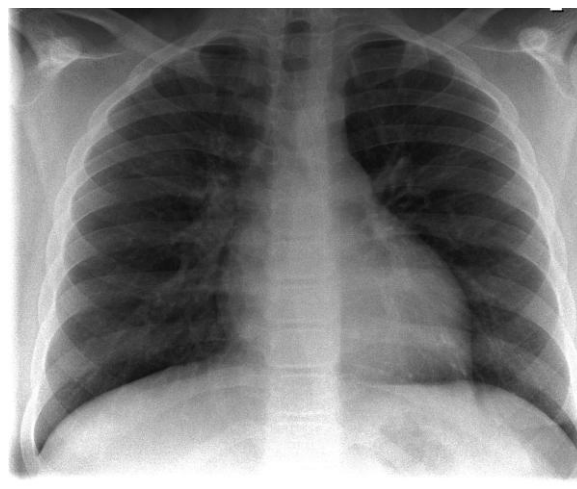
During sheath exchange, the long sheath was difficult to follow the wire at the groin and it was considered that access was lost. The procedure was ended and the patient returned to the catheterisation laboratory for fluoroscopic-guided valvuloplasty a few weeks later.

Immediately after screening it became apparent that there was a fine guide wire in the aorta extending up to the right carotid (Figures 8-3 and 8-4). A brief attempt was made to snare it in the mid descending aorta where it appeared to end. Closer observation revealed a minimally opaque section and then more wire extending down to the right femoral artery where the difficulties were encountered in the MRI lab. The attempt at snaring it ended when it became clear that the wire was extravascular for a significant portion (Figure 8-5). Snaring it from the carotid end was considered to be too risky for breakage and embolisation, hence it was left in situ. The carotid was widely patent in multiple views and after consultation with the vascular surgical team it was decided to leave the guide wire in place and not attempt surgical extraction of it. The patient subsequently had a successful X-Ray guided aortic valve balloon valvuloplasty without any complications. A few months later, the patient started having recurrent short episodes of cerebral transient ischaemic attacks. At that point it was decided to remove the guidewire surgically, which took place uneventfully via a left thoracotomy.

The clinical trial was discontinued after the complication in this last patient and the adverse event was reported to the Regulatory Authority. Although robust testing regarding wire fracture had been performed during the pre-clinical trial period as outlined in Chapter 5, (and further presented in the Appendix), it was concluded that the fibreglass guidewire was prone to breakage when direct force was applied. To this end, it was considered unsafe to

continue using this particular guidewire in the MRI environment and the clinical trial was discontinued.

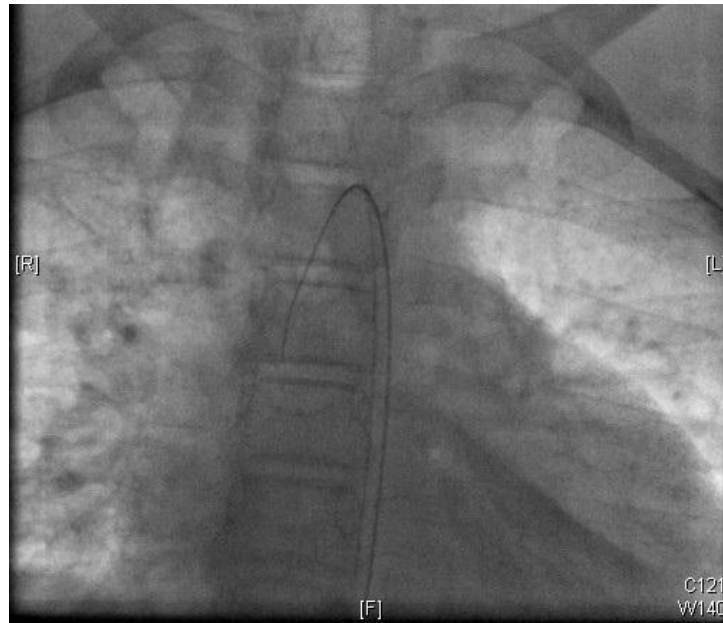
Other limitations encountered during the clinical trial were occasional suboptimal visualisation of the fibreglass wire, particularly at its nitinol tip and also poor steering around vascular curves and going around the arch to the ascending aorta, such as in clinical case 3 described above and also the last study patient. Artifacts from the iron markers were not encountered and the frame rate of 11-12 frames/sec obtained during interactive screening was adequate for visualisation and guidance of the interventional procedures.



**Figure 8-3.**

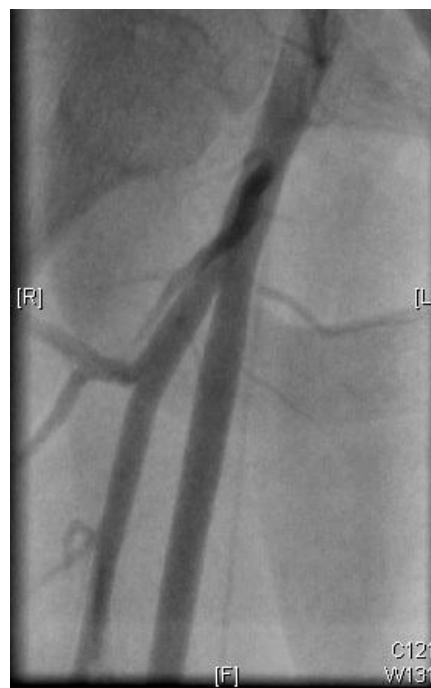
CXR of the patient prior to the balloon valvuloplasty procedure shows the fractured guidewire extending up the right carotid. This was not clearly noticed on the pre-catheterisation work-up.





**Figure 8-4.**

X-Ray fluoroscopy of the patient in the catheterisation lab shows the fractured guidewire extending up the right carotid and next to it a standard guidewire placed in the ascending aorta.



**Figure 8-5.** Femoral angiogram with the fractured guidewire in view, partially externalised outside the vessel.

### 8.3 Final discussion and future directions

In our institution combined MRI and cardiac catheterisation (hybrid XMR) studies, and also solely MRI-guided *diagnostic* cardiac catheterisations have been performed since 2002, with the aim of reducing the radiation exposure and acquiring all of the required anatomical and physiological information in one sitting.

The research work described in this thesis aimed at expanding the applications of XMR and MRI-guided diagnostic cardiac catheterisations and, most importantly, set the path towards materialisation of the first-in-man solely MR-guided interventions for congenital heart disease. Transcatheter cardiac therapeutic interventions prior to this research work had never become possible in humans, due to the lack of MRI compatible and safe cardiovascular equipment, mainly guidewires that are used for catheters, valvuloplasty or angioplasty balloons and for stents to travel on.

During this research work, preclinical assessment of a newly manufactured MRI compatible and safe guidewire was performed and cardiovascular interventions were performed on 6 animals (swine). Following approval by the UK Medicines and Healthcare products Regulatory Authority and the assigned Ethics committee the first in man solely MR-guided transcatheter cardiac interventions were successfully performed.

Several difficulties and limitations were encountered during materialisation of percutaneous paediatric interventions under MRI guidance. At the beginning of the interventional MRI programme we increased the number of diagnostic MRI-guided catheterisations in order to acquaint ourselves with catheterising without direct fluoroscopy. The duration and technique of catheterisation under MRI-guidance differed to an extent in comparison with the X-Ray fluoroscopy guided catheterisations. The shaft of the wedge catheter would for example some times loop back on itself and despite it being advanced outside the body we could not see the CO<sub>2</sub> filled balloon being advanced. In these cases we would have to withdraw the catheter, even outside the body and start advancing the catheter again. The inability of visualising the shaft of the catheters has been a major disadvantage and one that would increase at times the duration of the procedure. In addition, the nitinol tip of the MRI compatible guidewire was not visible, despite adapting and changing the slice orientation. To this end, we often had to make an assumption of its peripheral position. It was also not possible to shape and curve the body of the wire, hence its inability to turn around the aortic arch. In two patients that took part in the clinical trial, one with native aortic coarctation and a second one with severe aortic stenosis this was a significant disadvantage and the second of these patients had to have the procedure completed under X-Ray fluoroscopy. The inability to screen the wire down the

groin during sheath exchange in the last patient, made it also difficult to prevent the complication observed.

Median procedure and catheterisation times for MR-guided interventions were 180 and 110 min, which was longer than the equivalent X-Ray guided procedure. Communication amongst staff was occasionally difficult due to the noise produced during interactive scanning.

However, this was bypassed by good case preparation and having clearly defined roles in the team, who all knew well the steps of the procedure.

Another limitation of the MR-guided procedures is the occupational exposure to radiofrequency. In the MRI environment there are various magnetic fields present (high static field, gradient field and radio frequency field). When a measurement setup was developed for simultaneous measurements of gradient magnetic fields and magnetic fields generated by motion of the body in static fields and the values were compared to reference levels given by the International Commission on Non-Ionizing Radiation Protection (ICNIRP), the exposure significantly exceeded the reference levels in positions where the medical personnel could have access during interventional procedures <sup>74</sup>.

The pioneering research of our group and the extension of it towards materialisation of the first-in-man MRI guided interventions (<sup>2, 75-78</sup> and published abstracts 1-6) opened the horizons for further studies and attempts on optimising the equipment and sequences available to be used in the MRI environment and therefore bypass the limitations mentioned above. Indeed, in the past decade there is a very strong interest in the cardiovascular community in interventional MRI research <sup>79</sup>. Beyond the *passive catheter tracking* and navigation (used in our research work), and the *active catheter tracking*, researchers have also used *magnetic catheter steering*, whereby the catheter has a coil at its tip and can be deflected for easier navigation <sup>80,81</sup>. Magnetic catheter steering relies on a magnetic moment created by application of an electrical current to copper coils on the catheter tip, which results in alignment of the catheter in the direction of the Bo field and may be found to be more helpful in assisting MR-guided interventions in the future.

Recent work by the NIH group has demonstrated the feasibility of real-time MRI-guided right heart catheterisation in adults using *passive catheters* <sup>82</sup>. The MRI catheterisation procedure times were comparable with the X-Ray procedure times. The gadolinium-filled, rather than air-filled balloons seemed to be more conspicuous and therefore more effective in steering round to the target lesion. In addition, *“passive” commercial MRI needles* that are visualised based on intrinsic material properties have been used to access the pericardium or the cardiac cavities directly. Beyond the passive MRI needle, an investigational *“active” antenna-needle*

has also been used<sup>83</sup>. Both passive and active needles may enable more sophisticated non-surgical treatments for structural heart disease, including direct transthoracic implantation of large appliances and valves into the heart, non-surgical access and closure of large transthoracic cardiac access ports and enhanced image guidance of peripheral artery interventions such as recanalization of total chronic occlusion<sup>84-86</sup>.

Stent placement, valvar replacement, atrial septal defect closure, radiofrequency ablation and local gene cell delivery have all been shown to be feasible under sole MRI guidance in animals<sup>44-58</sup>, whilst balloon valvuloplasty and angioplasty became possible in humans<sup>77</sup>. Further availability of MR safe and compatible devices is essential for the success of invasive cardiovascular procedures performed under MRI-guidance and interactive visualisation of ablation lesions<sup>87</sup>.

In addition to the MRI-compatible and safe equipment being developed, novel imaging sequences have also emerged. A *novel flow visualisation method*, called virtual dye angiography has been developed recently in order to facilitate blood flow visualisation immediately and interactively in selected regions, analogous to selective catheter angiography<sup>88</sup>. Normal or pathological communications between specific heart chambers and vessels can be seen in this way. Phase-contrast velocity mapping would not be suitable for this purpose as it requires too much data and is not capable of determining directly if blood originating in one location travels to a nearby location. Virtual dye angiography uses two-dimensional radio frequency pulses to achieve interactive, intermittent, targeted saturation of a localized region of the blood pool. The flow of the saturated spins is observed directly on real-time images or, in an enhanced manner, using ECG synchronized background subtraction. The modular nature of the technique allows for easy and seamless integration into a real-time, interactive imaging system.

With the new MRI sequences being developed, that are targeted to serve real-time MRI procedures, and the emergence of new appropriate equipment, MR-guided procedures are expected to become less costly, far less invasive, faster and radiation-free. This may influence patient recovery and hospitalisation times.

XMR procedures in the meantime continue to have a very important role in the diagnosis and management of patients with congenital heart disease. The recent availability of a new hybrid system with side-by-side 1.5T magnet and C-arm X-Ray, may lead to more usage of the MRI as an interventional tool for the assessment and guidance of cardiac interventions.

In summary, interventional MRI either as sole-MRI guidance for percutaneous

procedures or as hybrid XMR procedures has many benefits to offer, from minimising radiation and providing imaging with great anatomical detail to facilitating analysis of complex physiology in patients with congenital heart disease. A big step forward has been achieved by materialising the world-first percutaneous cardiovascular interventions in patients with valvar or vascular stenosis. Further work continues in the field in our department and several other centres around the world.

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## **APPENDIX**

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RF-safe guidewire essential requirements checklist

Risk analysis

Technical information on Soluble Kollidon

Wire sterilization proforma

Wire instructions for use

Research Ethics Committee approval

Guy's & St. Thomas' Hospital Trust R & D approval

MHRA approval

Patient information leaflet

Children's information leaflet

Information for parents of children undergoing cardiac catheterisation

Clinical trial consent form

**CONTRACT MEDICAL INTERNATIONAL  
ESSENTIAL REQUIREMENTS CHECKLIST**

FILE ECO-00985/TF-0018  
NUMBER: \_\_\_\_\_

FILE NAME: MR Safe Guide Wire

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
<b>I. GENERAL REQUIREMENTS</b>					
1. The device must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>RK-031 Risk Management File for MR Safe Guide Wire</p> <p>Manufacturing Flow Chart</p> <p>ECO-00985-004: Pre-Clinical Animal Trial Testing</p>	<p>ISO 14971:2007 – Medical Devices – Application of Risk Management to Medical Devices</p> <p>CMI SOP ENG-007 “Risk Analysis Procedure”</p> <p>CMI SOP: RA-004 “General QA Inspection Procedure”</p> <p>CMI Inspection Specs.</p> <p>CMI SOP: ENG-002 “Device Master Records”</p> <p>Clinical Usage Requirements</p>	<p>Risk Management Section of Technical Dossier Body TF-0018</p> <p>Risk Management File in Risk Management Attachment of Technical Dossier TF-0018</p> <p>Manufacturing Flow Chart Attachment of Technical Dossier TF-0018</p> <p>Design Master Record Attachment of TF-0018, including inspection specifications</p> <p>Functional/Pre-clinical Testing Section of Technical Dossier TF-0018</p>

**CONTRACT MEDICAL INTERNATIONAL  
ESSENTIAL REQUIREMENTS CHECKLIST**

<b>Essential Requirement</b>	<b>A</b>	<b>N/ A</b>	<b>Compliance with the ER</b>	<b>Standards, Norms Applicable, Company Internal Procedures</b>	<b>Location of Documents: Comments:</b>
<p>2. The solutions adopted by the manufacturer for the design and construction of the devices must conform to safety principles, taking account of the generally acknowledged state of the art.</p> <p>In selecting the most appropriate solutions, the manufacturer must apply the following principles in the following order:</p> <ul style="list-style-type: none"> <li>• eliminate or reduce risks as far as possible (inherently safe design and construction),</li> <li>• where appropriate take adequate protection measures including alarms if necessary, in relation to risks that cannot be eliminated,</li> <li>• inform users of the residual risks due to any shortcomings of the protection measures adopted.</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>RK-031 Risk Management File for MR Safe Guide Wire</p> <p>Instructions for Use of MR Safe Guide Wire</p>	<p>ISO 14971:2007 – Medical Devices – Application of Risk Management to Medical Devices</p> <p>CMI SOP ENG-007 “Risk Analysis Procedure”</p>	<p>Risk Management Section of Technical Dossier Body TF-0018</p> <p>Risk Management File in Risk Management Attachment of Technical Dossier TF-0018</p> <p>Labeling and Instructions for Use Section of Technical Dossier</p>



**CONTRACT MEDICAL INTERNATIONAL  
ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement			A	N/ A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
3. The devices must achieve the performances intended by the manufacturer and be designed, manufactured and packaged in such a way that they are suitable for one or more of the functions referred to in Article 1 (2) (a), as specified by the manufacturer.			<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>Verification/Validations of MR Safe Guide wire device</p> <p>ECO-00985-002: Tensile Strength Test</p> <p>ECO-00985-003: Mechanical Flex and Fracture Test</p> <p>ECO-00985-004: Functional Animal Testing in vivo</p> <p>ECO-00985-005: ASTM testing of MR Guide Wire: RF-safety, MR image artifacts and magnetic interaction</p>	<p>ISO 11070: Sterile single-use intravascular catheter introducers</p> <p>Clinical Usage Requirements</p> <p>ASTM F2182 - 02a: Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging</p> <p>ASTM F2119 - 07 Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants</p> <p>ASTM F2213 - 06 Standard Test Method for Measurement of Magnetically Induced Torque on Medical Devices in the Magnetic Resonance Environment</p> <p>ISO 10993-1: 2003 "Biological evaluation of medical devices-Part 1: Evaluation and testing"</p> <p>ISO 11607-1:2006 Packaging for terminally sterilized medical devices – Part 1</p> <p>CMI SOPs</p> <p>CMI-set test standards</p>	<p>Summary of design verification / validation in main body of the Technical Dossier TF-0018</p> <p>Verifications/Validations/Testing Attachment of Technical Dossier TF-0018</p>
REG-F002	REV. 0	ISSUED: 17.10.08			SOP REF: REG-001	Page Number: S2 - 110 of S2 - 178	
					Pouch Sealing Validation of Packaging		

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Essential Requirement			A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
4. The characteristics and performances referred to in Sections 1, 2 and 3 must not be adversely affected to such a degree that the clinical conditions and safety of the patients and, where applicable, of other persons are compromised during the lifetime of the device as indicated by the manufacturer, when the device is subjected to the stresses which can occur during normal conditions of use.			<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>Age Testing NOT required as device is for clinical use</p> <p>Verification/Validations of MR Safe Guide wire device</p> <p>ECO-00985-002: Tensile Strength Test</p> <p>ECO-00985-003: Mechanical Flex and Fracture Test</p> <p>ECO-00985-004: Functional Animal Testing in vivo</p> <p>ECO-00985-005: ASTM testing of MR Guide Wire</p>	<p>ISO 11070: Sterile single-use intravascular catheter introducers Clinical Usage Requirements</p> <p>ASTM F2182 - 02a: Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging</p> <p>ASTM F2119 - 07 Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants</p> <p>ASTM F2213 - 06 Standard Test Method for Measurement of Magnetically Induced Torque on Medical Devices in the Magnetic Resonance Environment</p> <p>ISO 10993-1: 2003 "Biological evaluation of medical devices-Part 1: Evaluation and testing"</p> <p>ISO 11607-1:2006 Packaging for terminally sterilized medical devices – Part 1</p> <p>CMI SOPs</p> <p>CMI-set test standards</p>	<p>Summary of design verification / validation in main body of the Technical Dossier TF-0018</p> <p>Verifications/Validations/Testing Attachment of Technical Dossier TF-0018</p>
REG-F002	REV. 0	ISSUED: 17.10.08			SOP REF: REG-001	Page Number: S2 - 111 of S2 - 178	
					RF-safety, MR image artifacts and magnetic		

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Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
5. The devices must be designed, manufactured and packed in such a way that their characteristics and performances during their intended use will not be adversely affected during transport and storage taking account of the instructions and information provided by the manufacturer.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>RK-031 Risk Management File for MR Safe Guide Wire</p> <p>Pouch Sealing Verification Report</p> <p>Label</p> <p>Instructions for use</p>	<p>ISO 14971:2007 – Medical Devices – Application of Risk Management to Medical Devices</p> <p>CMI SOP ENG-007 “Risk Analysis Procedure”</p> <p>ISO 11607:2006</p> <p>ENG-017: CMI Pouch Sealing Validation SOP</p> <p>EN 980:2008 “Graphical symbols for use in the labeling of medical devices”</p> <p>EN 1041:1998 “Information supplied by the manufacturer with medical devices”</p>	<p>Risk Management Section of Technical Dossier Body TF-0018</p> <p>Risk Management File in Risk Management Attachment of Technical Dossier TF-0018</p> <p>See Packaging Qualification Section of Main Body of Technical Dossier TF-0018.</p> <p>Packaging Attachment of Technical Dossier TF-0018.</p> <p>Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018</p>

## CONTRACT MEDICAL INTERNATIONAL ESSENTIAL REQUIREMENTS CHECKLIST

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
6. Any undesirable side effect must constitute an acceptable risk when weighed against the performances intended.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Manufacturing Flow Chart	CMI SOP: RA-004 “General QA Inspection Procedure”	Manufacturing Flow Chart Attachment of Technical Dossier TF-0018
				CMI Inspection Specs.	Design Master Record Attachment of TF-0018, including inspection specifications
				CMI SOP: ENG-002 “Device Master Records”	
			RK-031 Risk Management File for MR Safe Guide Wire	ISO 14971:2007 – Medical Devices – Application of Risk Management to Medical Devices	Risk Management Section of Technical Dossier Body TF-0018
				CMI SOP ENG-007 “Risk Analysis Procedure”	Risk Management File in Risk Management Attachment of Technical Dossier TF-0018

**CONTRACT MEDICAL INTERNATIONAL  
ESSENTIAL REQUIREMENTS CHECKLIST**

<b>Essential Requirement</b>	<b>A</b>	<b>N/ A</b>	<b>Compliance with the ER</b>	<b>Standards, Norms Applicable, Company Internal Procedures</b>	<b>Location of Documents: Comments:</b>
<b>II. REQUIREMENTS REGARDING DESIGN AND CONSTRUCTION</b>  <b>7. Chemical, physical and biological properties</b>  <b>7.1</b> The devices must be designed and manufactured in such a way as to guarantee the characteristics and performances referred to in Section I on the General requirements. Particular attention must be paid to: <ul style="list-style-type: none"> <li>the choice of materials used, particularly as regards toxicity and, where appropriate flammability,</li> <li>the compatibility between the materials used and biological tissues, cells and body fluids, taking account of the intended purpose of the device.</li> </ul>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	ECO-00985-001: Biological and Functional Testing  ECO-00985-004: Functional Testing In Vivo	ISO 10993-1:2003 “Biological evaluation of medical devices- Part 1: Evaluation and testing”  Clinical Usage Requirements	Biocompatibility Section of Main Body of Technical File TF-0018.  Biocompatibility and Verifications/Validations Attachment of Technical File TF-0018

**CONTRACT MEDICAL INTERNATIONAL  
ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/ A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
7.2 The devices must be designed, manufactured and packed in such a way as to minimize the risk posed by contaminants and residues to the persons involved in transport, storage and use of the devices and to the patients, taking account of the intended purpose of the product. Particular attention must be paid to the tissues exposed and to the duration and frequency of exposure.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>Sterilization Validation: STVAL-0004</p> <p>RA-F028: Sterilization Adoption Questionnaire</p> <p>Routine Bioburden Testing Procedure</p>	<p>Sterilization: Validation completed to EN 550: Sterilization of medical devices. Validation and routine control of ethylene oxide sterilization with reference to:</p> <p>ISO 11135: Sterilization of Healthcare Products by Ethylene Oxide.</p> <p>CMI SOP: Bioburden Procedure QA-009</p> <p>Bioburden: ISO 11737-1: Sterilization of Medical devices- Microbiological Methods.</p>	<p>Refer to Sterilization Section in Main Body of Technical Dossier TF-0018</p> <p>Refer to Sterilization Attachment of TF-0018</p> <p>Refer to Bioburden Attachment of TF-0018</p> <p>Refer to Bioburden Statements in main technical file body TF-0018.</p>

**CONTRACT MEDICAL INTERNATIONAL  
ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
7.3 The devices must be designed and manufactured in such a way that they can be used safely with the materials, substances and gases with which they enter into contact during their normal use or during routine procedures; if the devices are intended to administer medicinal products they must be	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Manufacturing Flow Chart	CMI SOP: RA-004 “General QA Inspection Procedure”  CMI Inspection Specs.  CMI SOP: ENG-002 “Device Master Records”	Manufacturing Flow Chart Attachment of Technical Dossier TF-0018  Design Master Record Attachment of TF-0018, including inspection specifications
			Inspections	CMI inspection criteria  CMI SOP: RA-004 “General QA Inspection Procedure”	Refer to Device Master Record Attachment of Technical file TF-0018.
			ECO-00985-004: Functional Animal Testing In Vivo	Clinical Usage Requirements	Summary of design verification / validation in main body of the Technical Dossier TF-0018  Verifications/Validations/Testing Attachment of Technical Dossier TF-0018

## CONTRACT MEDICAL INTERNATIONAL ESSENTIAL REQUIREMENTS CHECKLIST

<b>Essential Requirement</b>	<b>A</b>	<b>N/ A</b>	<b>Compliance with the ER</b>	<b>Standards, Norms Applicable, Company Internal Procedures</b>	<b>Location of Documents: Comments:</b>
designed and manufactured in such a way as to be compatible with the medicinal products concerned according to the provisions and restrictions governing these products and that their performance is maintained in accordance with the intended use.			Device Design Specifications	ISO 11070: Sterile single-use intravascular catheter introducers  Design History File Device Master Record	Refer to Design Specification Section in Main Technical File Body of TF-0018  Refer to Device Master Record Attachment in TF-0018  Refer to Verifications and Validations Attachment in TF-0018
			RK-031 Risk Management File for MR Safe Guide Wire	ISO 14971:2007 – Medical Devices – Application of Risk Management to Medical Devices  CMI SOP ENG-007 “Risk Analysis Procedure”	Risk Management Section of Technical Dossier Body TF-0018  Risk Management File in Risk Management Attachment of Technical Dossier TF-0018



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ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
			Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018
7.4 There a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product as defined in Article I of Directive 65/65/EEC and which is liable to act upon the body with action ancillary to that of the device, the safety, quality and usefulness of the substance must be verified, taking account of the intended purpose of the device, by analogy with the appropriate methods specified in Directive 75/318/EEC.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	The device does not incorporate and is not considered a medicinal product. The device does not contain any materials that could be considered medicinal products.
7.5 The devices must be designed and manufactured in such a way as to reduce to a minimum the risks posed by substances leaking from the device.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	The device is a solid guide wire. There are no internal lumens or holes in the device. No fluid passes into or through the device. The device cannot leak.

**CONTRACT MEDICAL INTERNATIONAL  
ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
7.6 Devices must be designed and manufactured in such a way as to reduce, as much as possible, risks posed by the unintentional ingress of substances into the device taking into account the device and the nature of the environment in which it is intended to be used.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	ECO-00985-004: Functional Animal Testing In Vivo  Device Design Specifications  RK-031 Risk Management File for MR Safe Guide Wire	Clinical Usage Requirements  ISO 11070: Sterile single-use intravascular catheter introducers Design History File Device Master Record  ISO 14971:2007 – Medical Devices – Application of Risk Management to Medical Devices  CMI SOP ENG-007 “Risk Analysis Procedure”	Summary of design verification / validation in main body of the Technical Dossier TF-0018  Verifications/Validations/Testing Attachment of Technical Dossier TF-0018 Refer to Design Specification Section in Main Technical File Body of TF-0018  Refer to Device Master Record Attachment in TF-0018  Refer to Verifications and Validations Attachment in TF-0018 Risk Management Section of Technical Dossier Body TF-0018  Risk Management File in Risk Management Attachment of Technical Dossier TF-0018

**CONTRACT MEDICAL INTERNATIONAL  
ESSENTIAL REQUIREMENTS CHECKLIST**

<b>Essential Requirement</b>	<b>A</b>	<b>N/ A</b>	<b>Compliance with the ER</b>	<b>Standards, Norms Applicable, Company Internal Procedures</b>	<b>Location of Documents: Comments:</b>
			Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018

**CONTRACT MEDICAL INTERNATIONAL  
ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
<p>8. Infection and microbial contamination</p> <p>8.1 The devices and manufacturing processes must be designed in such a way as to eliminate or reduce as far as possible the risk of infection to the patient, user and third parties. The design must allow easy handling and, where necessary, minimize contamination of the device by the patient or vice versa during use.</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>Sterilization Validation: STVAL-0004</p> <p>RA-F028: Sterilization Adoption Questionnaire</p> <p>Routine Bioburden Testing Procedure</p>	<p>Sterilization: Validation completed to EN 550: Sterilization of medical devices. Validation and routine control of ethylene oxide sterilization with reference to:</p> <p>ISO 11135: Sterilization of Healthcare Products by Ethylene Oxide.</p> <p>CMI SOP: Bioburden Procedure QA-009</p> <p>Bioburden: ISO 11737-1: Sterilization of Medical devices- Microbiological Methods.</p>	<p>Refer to Sterilization Section in Main Body of Technical Dossier TF-0018</p> <p>Refer to Sterilization Attachment of TF-0018</p> <p>Refer to Bioburden Attachment of TF-0018</p> <p>Refer to Bioburden Statements in main technical file body TF-0018.</p>

**CONTRACT MEDICAL INTERNATIONAL  
ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/ A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
			Manufacturing Flow Chart	CMI SOP: RA-004 “General QA Inspection Procedure”  CMI Inspection Specs.  CMI SOP: ENG-002 “Device Master Records”	Manufacturing Flow Chart Attachment of Technical Dossier TF-0018  Design Master Record Attachment of TF-0018, including inspection specifications
			Bioburden testing	SOP of CMI: ENG- 019 “Bioburden Procedure”	Sterilization Description in Main Technical File of TF-0018
			Pyrogen testing	SOP of CMI: ENG- 020 “LAL Testing Procedure”	Routine Bioburden Results maintained on file at CMI Sterilization Description in Main Technical File of TF-0018  Routine LAL Test Results kept on File at CMI

**CONTRACT MEDICAL INTERNATIONAL  
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Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
<p>8.2 Tissues of animal origin must originate from animals that have been subjected to veterinary controls and surveillance adapted to the intended use of the tissues.</p> <p>Notified Bodies shall retain information on the geographical origin of the animals.</p> <p>Processing, preservation, testing and handling of tissues, cells and substances of animal origin must be carried out so as to provide optimal security. In particular safety with regard to viruses and other transferable agents must be addressed by implementation of validated methods of elimination or viral inactivation in the course of the manufacturing process.</p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<p>Label</p> <p>Instructions for use</p> <p>N/A</p>	<p>EN 980:2008 “Graphical symbols for use in the labeling of medical devices”</p> <p>EN 1041:1998 “Information supplied by the manufacturer with medical devices”</p> <p>N/A</p>	<p>Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018</p> <p>The device is a guide wire that does not contain animal tissue of any kind. The device is composed only of non-tissue materials.</p>

**CONTRACT MEDICAL INTERNATIONAL  
ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
8.3 Devices delivered in a sterile state must be designed, manufactured and packed in a non-reusable pack and/or according to appropriate procedures to ensure they are sterile when placed on the market and remain sterile, under the storage and transport conditions laid down, until the protective packaging is damaged or opened.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>Sterilization Validation: STVAL-0004</p> <p>RA-F028: Sterilization Adoption Questionnaire</p> <p>Routine Bioburden Testing Procedure</p>	<p>Sterilization: Validation completed to EN 550: Sterilization of medical devices. Validation and routine control of ethylene oxide sterilization with reference to:</p> <p>ISO 11135: Sterilization of Healthcare Products by Ethylene Oxide.</p> <p>CMI SOP: Bioburden Procedure QA-009</p> <p>Bioburden: ISO 11737-1: Sterilization of Medical devices- Microbiological Methods.</p>	<p>Refer to Sterilization Section in Main Body of Technical Dossier TF-0018</p> <p>Refer to Sterilization Attachment of TF-0018</p> <p>Refer to Bioburden Attachment of TF-0018</p> <p>Refer to Bioburden Statements in main technical file body TF-0018.</p>

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ESSENTIAL REQUIREMENTS CHECKLIST**

<b>Essential Requirement</b>	<b>A</b>	<b>N/ A</b>	<b>Compliance with the ER</b>	<b>Standards, Norms Applicable, Company Internal Procedures</b>	<b>Location of Documents: Comments:</b>
			Pouch Sealing Verification Report	ISO 11607:2006  ENG-017: CMI Pouch Sealing Validation SOP	See Packaging Qualification Section of Main Body of Technical Dossier TF-0018.  Packaging Attachment of Technical Dossier TF-0018.



**CONTRACT MEDICAL INTERNATIONAL  
ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
8.4 Devices delivered in a sterile state must have been manufactured and sterilized by an appropriate, validated method.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>Sterilization Validation: STVAL-0004</p> <p>RA-F028: Sterilization Adoption Questionnaire</p> <p>Routine Bioburden Testing Procedure</p>	<p>Sterilization: Validation completed to EN 550: Sterilization of medical devices. Validation and routine control of ethylene oxide sterilization with reference to:</p> <p>ISO 11135: Sterilization of Healthcare Products by Ethylene Oxide.</p> <p>CMI SOP: Bioburden Procedure QA-009</p> <p>Bioburden: ISO 11737-1: Sterilization of Medical devices- Microbiological Methods.</p>	<p>Refer to Sterilization Section in Main Body of Technical Dossier TF-0018</p> <p>Refer to Sterilization Attachment of TF-0018</p> <p>Refer to Bioburden Attachment of TF-0018</p> <p>Refer to Bioburden Statements in main technical file body TF-0018.</p>

## CONTRACT MEDICAL INTERNATIONAL ESSENTIAL REQUIREMENTS CHECKLIST

<b>Essential Requirement</b>	<b>A</b>	<b>N/ A</b>	<b>Compliance with the ER</b>	<b>Standards, Norms Applicable, Company Internal Procedures</b>	<b>Location of Documents: Comments:</b>
8.5 Devices intended to be sterilized must be manufactured in appropriately controlled (e.g. environmental) conditions.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Manufacturing Flow Chart	CMI SOP: RA-004 “General QA Inspection Procedure”  CMI Inspection Specs.  CMI SOP: ENG-002 “Device Master Records”	Manufacturing Flow Chart Attachment of Technical Dossier TF-0018  Design Master Record Attachment of TF-0018, including inspection specifications
			Device is manufactured in an ISO 14698 and ISO 14644 controlled environment. CMI’s controlled environment is ISO Class 8.	ISO 14698 and 14644: Cleanrooms and associated controlled environments  CMI SOP: ENG-009 “GMP & Compliance with Quality System Procedures”  CMI SOP: QS-409 “Process Control”	Validation and Verification of Controlled Environment on File at CMI

**CONTRACT MEDICAL INTERNATIONAL  
ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
8.6 Packaging systems for non-sterile devices must keep the product without deterioration at the level of cleanliness stipulated and, if the devices are to be sterilized prior to use, minimize the risk of microbial contamination; the packaging system must be suitable taking account of the method of sterilization indicated by the manufacturer.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device is delivered sterile so packaging for non-sterile devices does not apply.
8.7 The packaging and/or label of the device must distinguish between identical or similar products sold in both sterile and non-sterile condition.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device is ONLY delivered sterile. Therefore no distinction between sterile and non-sterile products should be made.
9. Construction and environmental properties					
9.1 If the device is intended for use in combination with other devices or equipment, the whole combination, including the connection system must be safe and must not impair the specified performances of the devices. Any restrictions on use must be indicated on the label or in the instructions for use.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	RK-031 Risk Management File for MR Safe Guide Wire	ISO 14971:2007 – Medical Devices – Application of Risk Management to Medical Devices  CMI SOP ENG-007 “Risk Analysis Procedure”	Risk Management Section of Technical Dossier Body TF-0018  Risk Management File in Risk Management Attachment of Technical Dossier TF-0018

**CONTRACT MEDICAL INTERNATIONAL  
ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/ A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
			<p>ECO-00985-005: ASTM testing of MR Guide Wire: RF-safety, MR image artifacts and magnetic interaction</p> <p>ECO-00985-004: Animal Functional Testing In Vivo</p>	<p>Clinical Usage Requirements</p> <p>ASTM F2182 - 02a: Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging</p> <p>ASTM F2119 - 07 Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants</p> <p><i>ASTM F2213 - 06 Standard Test Method for Measurement of Magnetically Induced Torque on Medical Devices in the Magnetic Resonance Environment</i></p>	<p>Summary of design verification / validation in main body of the Technical Dossier TF-0018</p> <p>Verifications/Validations/Testing Attachment of Technical Dossier TF-0018</p>

## CONTRACT MEDICAL INTERNATIONAL ESSENTIAL REQUIREMENTS CHECKLIST

<b>Essential Requirement</b>	<b>A</b>	<b>N/ A</b>	<b>Compliance with the ER</b>	<b>Standards, Norms Applicable, Company Internal Procedures</b>	<b>Location of Documents: Comments:</b>
9.2 Devices must be designed and manufactured in such a way as to remove or minimize as far as is possible:					
• the risk of injury, in connection with their physical features, including the volume/pressure ratio, dimensional and where appropriate ergonomic features,	<input checked="" type="checkbox"/>	<input type="checkbox"/>	RK-031 Risk Management File for MR Safe Guide Wire	ISO 14971:2007 – Medical Devices – Application of Risk Management to Medical Devices  CMI SOP ENG-007 “Risk Analysis Procedure”	Risk Management Section of Technical Dossier Body TF-0018  Risk Management File in Risk Management Attachment of Technical Dossier TF-0018
• risks connected with reasonably foreseeable environmental conditions, such as magnetic fields, external electrical influences, electrostatic discharge, pressure, temperature or variations in pressure and acceleration,	<input checked="" type="checkbox"/>	<input type="checkbox"/>	RK-031 Risk Management File for MR Safe Guide Wire	ISO 14971:2007 – Medical Devices – Application of Risk Management to Medical Devices  CMI SOP ENG-007 “Risk Analysis Procedure”	Risk Management Section of Technical Dossier Body TF-0018  Risk Management File in Risk Management Attachment of Technical Dossier TF-0018
• the risks of reciprocal interference with other devices normally used in the investigations or for the treatment given,	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not deliver or produce any signals that would produce a reciprocal interface.

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ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
<ul style="list-style-type: none"> <li>risks arising where maintenance or calibration are not possible (as with implants), from aging of the materials used or loss of accuracy of any measuring or control mechanism.</li> </ul>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not contain any calibration because the device cannot measure in any way.
9.3 Devices must be designed and manufactured in such a way as to minimize the risks of fire or explosion during normal use and in single fault condition. Particular attention must be paid to devices whose intended use includes exposure to flammable substances or to substances which could cause combustion	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Guide wire does not contain any flammable materials, and there are no influences that the device is exposed to during use that would cause the device to explode.
10. Devices with a measuring function					
10.1 Devices with a measuring function must be designed and manufactured in such a way as to provide sufficient accuracy and stability within appropriate limits of accuracy and taking account of the intended purpose of the device. The limits of accuracy must be indicated by the manufacturer.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Guide wire does not contain a measuring function.
10.2 The measurement, monitoring and display scale must be designed in line with ergonomic principles, taking account of the intended purpose of the device.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Guide wire does not contain a measuring function.

**CONTRACT MEDICAL INTERNATIONAL  
ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
10.3 The measurements made by devices with a measuring function must be expressed in legal units conforming to the provisions of Council Directive 80/181/EEC, as last amended by Directive 89/617/EEC.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Guide wire does not contain a measuring function.
11. Protection against radiation	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not emit any radiation.
11.1 General					
11.1.1 Devices shall be designed and manufactured such that exposure of patients, users and other persons to radiation shall be reduced as far as possible compatible with the intended purpose, whilst not restricting the application of appropriate specified levels for therapeutic and diagnostic purposes.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not emit any radiation.

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ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
11.2 Intended radiation					
11.2.1 Where devices are designed to emit hazardous levels of radiation necessary for a specific medical purpose the benefit of which is considered to outweigh the risks inherent in the emission, it must be possible for the user to control the emissions. Such devices shall be designed and manufactured to ensure reproducibility and tolerance of relevant variable parameters.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not emit any radiation.
11.2.2 Where devices are intended to emit potentially hazardous, visible and/or radiation, they must be fitted, where practicable, with visual displays and/or audible warnings of such emissions.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not emit any radiation.
11.3 Unintended radiation					
11.3.1 Devices shall be designed and manufactured in such a way that exposure of patients, users and other persons to the emission of unintended, stray or scattered radiation is reduced as far as possible.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not emit any radiation.



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ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
11.4 Instructions					
11.4.1 The operating instructions for devices emitting radiation must give detailed information as to the nature of the emitted radiation, means of protecting the patient and the user and on ways of avoiding misuse and of eliminating the risks inherent in installation.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not emit any radiation.
11.5 Ionizing radiation					
11.5.1 Devices intended to emit ionizing radiation must be designed and manufactured in such a way as to ensure that, where practicable, the quantity, geometry and quality of radiation emitted can be varied and controlled taking into account the intended use.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not emit any radiation.
11.5.2 Devices emitting ionizing radiation intended for diagnostic radiology shall be designed and manufactured in such a way as to achieve appropriate image and/or output quality for the intended medical purpose whilst minimizing radiation exposure of the patient and user.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not emit any radiation.

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ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
11.5.3 Devices emitting ionizing radiation, intended for therapeutic radiology shall be designed and manufactured in such a way as to enable reliable monitoring and control of the delivered dose, the beam type and energy and where appropriate the quality of radiation.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not emit any radiation.
12. Requirements for medical devices connected to or equipped with an energy source	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device is not equipped with or connected to an energy source.
12.1 Devices incorporating electronic programmable systems must be designed to ensure the repeatability, reliability and performance of these systems according to their intended use. In the event of a single fault condition (in the system) appropriate means should be adopted to eliminate or reduce as far as possible consequent risks.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device is not equipped with or connected to an energy source.
12.2 Devices where the safety of the patients depends on an internal power supply must be equipped with a means of determining the state of the power supply.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device is not equipped with or connected to an energy source.
12.3 Devices where the safety of the patients depends on an external power supply must include an alarm system to signal any power failure.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device is not equipped with or connected to an energy source.

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ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
12.4 Devices intended to monitor one or more clinical parameters of a patient must be equipped with appropriate alarm systems to alert the user of situations which could lead to death or severe deterioration of the patient's state of health.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device is not equipped with or connected to an energy source.
12.5 Devices must be designed and manufactured in such a way as to minimize the risks of creating electromagnetic fields which could impair the operation of other devices or equipment in the usual environment.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device is not equipped with or connected to an energy source.
12.6 Protection against electrical risks Devices must be designed and manufactured in such a way as to avoid, as far as possible, the risk of accidental electric shocks during normal use and in single fault condition, provided the devices are installed correctly.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device is not equipped with or connected to an energy source.

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ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
12. 7 Protection against mechanical and thermal risks					
12.7.1 Devices must be designed and manufactured in such a way as to protect the patient and user against mechanical risks connected with, for example, resistance, stability and moving parts.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not contain any moving parts or mechanical structures.
12.7.2 Devices must be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from vibration generation by the devices, taking account of technical progress and of the means available for limiting vibrations, particularly at source, unless the vibrations are part of the specified performance.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not contain any moving parts or mechanical structures.
12.7.3 Devices must be designed and manufactured in such a way as to reduce to the lowest possible level the risks arising from the noise emitted, taking account of technical progress and of the means available to reduce noise, particularly at source, unless the noise emitted is part of the specified performance.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not contain any moving parts or mechanical structures.

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Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
12.7.4 Terminals and connectors to the electricity, gas or hydraulic and pneumatic energy supplies which the user has to handle must be designed and constructed in such a way as to minimize all possible risks.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not contain an energy supply.
12.7.5 Accessible parts of devices (excluding any parts or areas intended to supply heat or reach given temperatures) and their surroundings must not attain potentially dangerous temperatures under normal use.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	ECO-00985-005: ASTM testing of MR Guide Wire: RF-safety, MR image artifacts and magnetic interaction	<p>ASTM F2182 - 02a: Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging</p> <p>ASTM F2119 - 07 Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants</p> <p><i>ASTM F2213 - 06 Standard Test Method for Measurement of Magnetically Induced Torque on Medical Devices in the Magnetic Resonance Environment</i></p>	

**CONTRACT MEDICAL INTERNATIONAL  
ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
12.8 Protection against the risks posed to the patient by energy supplies or substances.					
12.8.1 Devices for supplying the patient with energy or substances must be designed and constructed in such a way that the flow-rate can be set and maintained accurately enough to guarantee the safety of the patient and of the user.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device cannot supply patient with energy or substances.
12.8.2 Devices must be fitted with the means of preventing and/or indicating any inadequacies in the flow-rate which could pose a danger.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device cannot supply patient with energy or substances.
Devices must incorporate suitable means to prevent, as far as possible, the accidental release of dangerous levels of energy from an energy and/or substance source.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device cannot supply patient with energy or substances.
12.9 The function of the controls and indicators must be clearly specified on the devices.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not contain any controls or indicators. No instructions are marked on the device.

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ESSENTIAL REQUIREMENTS CHECKLIST**

<b>Essential Requirement</b>	<b>A</b>	<b>N/ A</b>	<b>Compliance with the ER</b>	<b>Standards, Norms Applicable, Company Internal Procedures</b>	<b>Location of Documents: Comments:</b>
Where a device bears instructions required for its operation or indicates operating or adjustment parameters by means of a visual system, such information must be understandable to the user and, as appropriate, the patient.					

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ESSENTIAL REQUIREMENTS CHECKLIST**

<b>Essential Requirement</b>	<b>A</b>	<b>N/ A</b>	<b>Compliance with the ER</b>	<b>Standards, Norms Applicable, Company Internal Procedures</b>	<b>Location of Documents: Comments:</b>
<p>13. Information supplied by the manufacturer</p> <p>13.1 Each device must be accompanied by the information needed to use it safely and to identify the manufacturer, taking account of the training and knowledge of the potential users.</p> <p>This information comprises the details on the label and the data in the instructions for use.</p> <p>As far as practicable and appropriate, the information needed to use the device safely must be set out on the device itself and/or on the packaging for each unit or, where appropriate, on the sales packaging. If individual packaging of each unit is not practicable, the information must be set out in the leaflet supplied with one or more devices.</p> <p>Instructions for use must be included in the packaging for every device. By way of exception, no such instructions for use are needed for devices in Class I or Class IIa if they can be used safely without any such instructions.</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>Label</p> <p>Instructions for use</p>	<p>EN 980:2008 “Graphical symbols for use in the labeling of medical devices”</p> <p>EN 1041:1998 “Information supplied by the manufacturer with medical devices”</p>	<p>Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018</p>



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ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
13.2 Where appropriate, this information should take the form of symbols. Any symbol or identification colour used must conform to the harmonized standards. In areas for which no standards exist, the symbols and colours must be described in the documentation supplied with the device.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018
13.3 The label must bear the following particulars:  a) the name or trade name and address of the manufacturer. For devices imported into the Community, in view of their distribution in the Community, the label, or the outer packaging, or the instructions for use, shall contain in addition the name and address of either the person responsible referred to in Article 14(2) or of the authorized representative of the manufacturer established within the Community or of the importer established within the Community, as appropriate;	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018

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ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
b) the details strictly necessary for the user to identify the device and the contents of the packaging;	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018
c) where appropriate, the word STERILE;	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018

**CONTRACT MEDICAL INTERNATIONAL  
ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
d) where appropriate, the batch code, preceded by the word LOT or the serial number;	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018
e) where appropriate, an indication of the date by which the device should be used, in safety, expressed as the year and month;	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018

**CONTRACT MEDICAL INTERNATIONAL  
ESSENTIAL REQUIREMENTS CHECKLIST**

Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
f) where appropriate, an indication that the device is for single use;	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018
g) if the device is custom-made, the words custom made device;	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device is not custom made. Device is produced with a standard specification.
h) if the device is intended for clinical investigations, the words exclusively for clinical investigations;	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018

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Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
i) any special storage and/or handling conditions;	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018
j) any special operating instructions;	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	There are no special operating instructions that would require placement on the label of the device.
k) any warnings and/or precautions to take;	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018
l) year of manufacture for active devices other than those covered by e). This indication may be included in the batch or serial number;	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device is not an active device.

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Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
m) where applicable, method of sterilization.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018
13.4 If the intended purpose of the device is not obvious to the user, the manufacturer must clearly state it on the label and in the instructions for use.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018
13.5 Wherever reasonable and practicable, the devices and detachable components must be identified, where appropriate in terms of batches, to allow all appropriate action to detect any potential risk posed by the devices and detachable components.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not contain any detachable components. Device is single guidewire.

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Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
13.6 Where appropriate, the instructions for use must contain the following particulars:					
a) the details referred to in 13.3, with the exception of d) and e);	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018
b) the performances referred to in Section 3 and any undesirable side-effects;	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018

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Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
c) if the device must be installed with or connected to other medical devices or equipment in order to operate as required for its intended purpose, sufficient details of its characteristics to identify the correct devices or equipment to use in order to obtain a safe combination;	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018
d) all the information needed to verify whether the device is properly installed and can operate correctly and safely, plus details of the nature and frequency of the maintenance and calibration needed to ensure that the devices operate properly and safely at all times;	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018
e) where appropriate, information to avoid certain risks in connection with implantation of the device;	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device is not implantable.
f) information regarding the risks of reciprocal interference posed by the presence of the device during specific investigations or treatment;	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not emit any signal that would create a reciprocal interface.



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Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
g) the necessary instructions in the event of damage to the sterile packaging and, where appropriate, details of appropriate methods of re-sterilization;	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018
h) if the device is reusable, information on the appropriate processes to allow reuse, including cleaning, disinfection, packaging and, where appropriate, the method of sterilization of the device to be resterilized, and any restriction on the number of reuses.  Where devices are supplied with the intention that they can be sterilized before use, the instructions for cleaning and sterilization must be such that, if correctly followed, the device will still comply with the requirements in Section I;	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device is Single Use Only.
i) details of any further treatment or handling needed before the device can be used (for example, sterilization, final assembly, etc.);	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not require any assembly or special handling before use.

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Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
j) in the case of devices omitting radiation for medical purposes, details of the nature, type, intensity and distribution of this radiation.  The instructions for use must also include details allowing the medical staff to brief the patient on any contra-indications and any precautions to be taken. These details should cover in particular:	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not emit any radiation.
k) precautions to be taken in the event of changes in the performance of the device;	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018

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Essential Requirement	A	N/A	Compliance with the ER	Standards, Norms Applicable, Company Internal Procedures	Location of Documents: Comments:
l) precautions to be taken as regards exposure, in reasonably foreseeable environmental conditions, to magnetic fields, external electrical influences, electrostatic discharge, pressure or variations in pressure, acceleration, thermal ignition sources, etc.;	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Label  Instructions for use	EN 980:2008 “Graphical symbols for use in the labeling of medical devices”  EN 1041:1998 “Information supplied by the manufacturer with medical devices”	Labels located in Labels and Instructions For Use Attachment of Technical File TF-0018
m) adequate information regarding the medicinal product or products which the device in question is designed to administer, including any limitations in the choice of substances to be delivered;	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device is not capable or intended to deliver medicinal products.
n) precautions to be taken against any special, unusual risks related to the disposal of the device;	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not require any special disposal.
o) medicinal substances incorporated into the devices as an integral part in accordance with Section 7.4;	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device is not capable or intended to deliver medicinal products.
p) degree of accuracy claimed for devices with a measuring function.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device does not contain a measuring function.

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ESSENTIAL REQUIREMENTS CHECKLIST**

<b>Essential Requirement</b>	<b>A</b>	<b>N/ A</b>	<b>Compliance with the ER</b>	<b>Standards, Norms Applicable, Company Internal Procedures</b>	<b>Location of Documents: Comments:</b>
14. Where conformity with the essential requirements must be based on clinical data, as in Section 1 (6), such data must be established in accordance with Annex X.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	N/A	N/A	Device is being used for clinical testing. Data will be established according to Annex X, however conformity is not applicable at this stage.

## Technical Documentation

Risk management / Market observation / **Risk analysis**

### In vitro Physical/Mechanical Testing:

Test and Description	Standard for Test	Results	Acceptance Criteria
Test for Fracture of Guide Wires	ISO 11070: Sterile Single Use intravascular catheter introducers: Annex F	Passed with no signs of deformation. No cracking or breakage of wire	No signs of fracture and no flaking of the coating
Flexibility Test	ISO 11070: Sterile Single Use intravascular catheter introducers: Annex G	Guide wire displayed flexible behavior and had no defects after being subjected to the flexibility test	No signs of defects or damage and no flaking of the coating
Sliding Properties	N/A	Device was found to have low friction when being slid in a phantom set up.	N/A
Strength Test	ISO 11070: Sterile Single Use intravascular catheter introducers: Annex H	Passed	Breaking Force of More than 10 Newtons
ASTM testing of MR Guide Wire: RF-safety, MR image artifacts and magnetic interaction	ASTM F2182 - 02a: Standard Test Method for Measurement of Radio Frequency Induced Heating Near Passive Implants During Magnetic Resonance Imaging  ASTM F2119 - 07 Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants  <i>ASTM F2213 - 06 Standard Test Method for Measurement of Magnetically Induced Torque on Medical Devices in the Magnetic Resonance Environment</i>	No significant heating beyond global SAR related tissue heating was found. Maximum temperature increase observed was 0.3°C at maximum scanner power (4W/kg).	There were no set acceptance criteria of this standard

## Technical Documentation

Risk management / Market observation / **Risk analysis**

Product (-group): « <b>Productgroup</b> »	Product (-group)-No.: « <b>Productno.</b> »
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### Risk analysis

Pos	Interface/System	Potential Hazard	Cause of Hazard	Consequence	Probability A	Severity B	Probability of detection E	Risk priority number (A x B x E)	Safety measure/Comment	A	B	E	RPZ	R
<b>1</b>	<b>Toxicologic hazards (Materials and substances)</b>													
1.1	complete guidewire	Release of toxic agents	Materials or components with toxic effect	Allergic reaction; danger of poisoning	2	7	2	28	Proper material selection (cf. Documentation of materials); incoming goods inspection, Enclosure of hazardous materials	1	7	1	7	yes
<b>2</b>	<b>Hazards due to energy and contributing factors</b>													
2.1	fracture of guidewire	required replacement of guidewire	Material defect, processing defect, application error	Prolongation of Intervention	2	6	2	24	Validated production/manufacturing processes; in-process-control; final inspection, instructions for use, safety by appropriate construction	1	6	1	6	yes
2.2	loss of wire segment	vascular occlusion	material defect, processing defect, application error	vessel damage; surgical repair	2	6	2	24	Safety by protective tubing	1	6	1	6	yes
2.3	vessel perforation	vascular injury and bleeding	Stiffness of tip section too high	surgical repair					Reduction of the stiffness of the tip section, atraumatic rounded tip shape					
<b>3</b>	<b>Biological hazards and contributing factors</b>													
3.1	complete guidewire	Elevated biological contamination -> non-sterility	Inappropriate production environment	infection	2	5	2	20	Production under controlled conditions	1	5	1	5	yes

Document-No.: «Produktnr»\_Tzifa Thesis for King's College page 155 of 3 Revision: 00 Valid from: «gültig»

Creation: ..... Verified/Approved: .....  
Signature Signature

## Technical Documentation

Risk management / Market observation / Risk analysis														
3.2	complete guidewire	Non-sterility	Inappropriate sterilization process Sterilisationsprozess	infection	2	5	2	20	Usage of validated sterilization cycle	1	5	1	5	yes
3.3	complete guidewire	non-sterility	leak in sterile packaging; inappropriate sealing of packaging	infection	2	5	2	20	Validated packaging process; internal process control of production process;Note in label and instructions for use	1	5	1	5	yes
3.4	sterile packaging	non-sterilty	damaged sterile packagingg	infection	2	5	2	20	Appropriate packaging material; Note in label and instructions for use	1	5	1	5	yes
4	Environmental hazards and contributing factors													
	no known hazards													
5	Hazards due to delivery of energy or substances													
5.1	not relevant													
6	Hazards related to the usage of the product													
6.1	guidewire	vessel perforation	misuse	surgical repair	2	7	2	32	instructions for use	1	7	1	7	yes
7	Inappropriate, insufficient or too complicated user interfaces (man-machine communication)													
7.1	guidewire	sticking of the guidewire	incompatible guide catheter	exchange of components and devices, prolongation of intervention	2	5	2	20	Information on appropriate guide catheter type & size, remark in instructions for use	1	5	1	5	yes
8	Hazards due to malfunction, wrong maintenace and deterioration and contributing factors													
8.1	guidewire	non-sterility	storage beyond expiration date of sterile packaging	infection	1	5	2	10	Indication of expiration date in label	1	5	1	5	yes
8.2	guidewire	material brittle and crack formation (potential fracture)	storage beyond expiration date of sterile packaging	Surgical repair	2	7	2	28	Indication of expiration date in label	1	5	1	5	yes

## Technical Documentation

Risk management / Market observation / Risk analysis												

A = probability of occurrence (1-10) low-high/B = Severity (1-10)low-high/E =Probability of detection (1-10) low-high/RZP = Risk priority number (A\*B\*E)/ R = Risk acceptance (Yes/No)

### Risk assessment

Further risk mitigation not required.

### *Risk management (applicable in case of required further risk mitigation, safety measures described in supplementary document)*

1. Risk mitigation
2. Analysis of options (Determination of measures)
3. Implementation of measures
4. Assessment of residual risk
5. Risk/benefit analysis
6. Consideration of further hazards

### *Overall residual risk assessment*

The overall residual risk is acceptable, because the benefit exceeds the residual risks.

### *Risk management report*

Cf. document „Risk management report“ as part of the technical documentation.

The risk analysis was performed by:

Title / Surname / Name	Function / Qualification	Signature









# STERILISATION PRO-FORMA APPLIED FOR DEVICE(S) UNDERGOING CLINICAL TRIAL

**Company Name :** *Contract Medical International GmbH*

**Model Name :** *MR Safe Guidewire*

**Model Number :** *MG-35180-001*

**Description :** *Guidewire for MR applications*

<b>1. Is the device made for:-</b> Single use Re – use		<i>Single Use</i>
<b>2. Will the device be provided sterile</b>	<i>YES</i>	<i>If yes continue with question 3 if not go to question 8.</i>
<b>3. Is the device sterilized by the:-</b>  Manufacturer  Sub-contractor	<i>Sub-Contractor</i>	Please provide details of sterilization facility e.g. name, location, process  Medical-Produkte Lichtenberg GmbH (MPL) Gewerbegebiet Süd 18 09618 Brand-Erbisdorf Germany Phone: 03732252590 Ethylene Oxide Cycle 1.1
<b>4. By what method is the device sterilized</b>  Radiation, Gamma or Electron Beam Ethylene Oxide Steam Dry Heat Chemical Other	<i>Ethylene Oxide</i>	Please provide proof of process validation, e.g. results, certificates and justification for choice of sterilization process  <i>See Attached Sterilization Validation STVAL-0004</i>

		<p><i>NOTE: Attachment 1 contains the Summary of the Validation as well as the internal report. The complete report is on file at Contract Medical International GmbH.</i></p>
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<p><b>5. What records for product release are available:-</b></p> <p><b>Indicator testing:-</b>  <b>Chemical</b>  <b>Biological</b>  <b>Dosimetric release</b>  <b>Parametric release</b></p>	<p><i>Product falls under Contract Medical's Worst Case Kit, so separate sterilization validation is not required</i></p>	<p><b><i>Please provide appropriate information e.g. results and outcome</i></b></p> <p><i>Biological Indicator Testing and Parametric release are routine sterility criteria. The results are evaluated by CMI and MPL with release of each batch.</i></p> <p><i>See Attached Sterilization Validation STVAL-0004 and Sterilization Verification ECO-0933.</i></p>
<p><b>6. Have bioburden determinations been undertaken</b></p>	<p><i>Part will be routinely bioburden tested on a per lot basis.</i></p>	<p><b><i>Please provide information e.g. type (nature), frequency, results, outcome</i></b></p> <p><i>Device is tested to ISO 11737-1 Sterilization of Medical devices- Microbiological Methods.</i></p> <p><i>Using the membrane filtration Method and examined for bacteria, spores, and funghi.</i></p> <p><i>Every lot of product will be tested.</i></p> <p><i>Results are not yet available for clinical trial lot; however, bioburden will be reviewed internally before the product is</i></p>

		<p><i>released and the results will comply with CMI's Sterilization Validation, STVAL-0004.</i></p>
<p><b>7. Are environmental precautions undertaken on the device during:</b></p> <p><b>Manufacturing Sterilization</b></p>	YES	<p><b><i>Please provide information e.g. type of controls, frequency of monitoring, results and outcome</i></b></p> <p><i>Manufacturing: Device is manufactured in an ISO 14698 and ISO 14644 controlled environment. CMI's controlled environment is ISO Class 8.</i></p> <p><i>Types of Controls: Microbiological Monitoring: 1 x per month Particle Monitoring: 1 x per week Environmental (Temperature, Humidity, Pressure): 1 x per day</i></p> <p><i>Results and Outcome: Results are trended on a time basis. Results are evaluated via alert and action levels. All results are within ISO and Good Manufacturing Practice limits.</i></p> <p><i>Sterilization: Device is packaged in a sealed pouch before leaving the controlled environment. Sterilizer is EN ISO 9002/07.94 and EN46002/08.96 certified.</i></p>
<p><b>8. If the device is not provided sterile will it:-</b></p>		<p><i>If device is not required to be sterilized do not</i></p>

<p>a. Be sterilized at point of use</p> <p>b. Device is not required to be sterilized</p>	N/A	<i>continue</i>
<p>9. If the device is to be sterilized at point of use: By what method:-</p> <p>Steam</p> <p>Chemical</p> <p>Other</p>	N/A	<p>Please provide proof of process validation,</p> <p><i>e.g. results, certificates and justification for choice of sterilization process</i></p>
<p>10. Are reprocessing instructions available:-</p> <p>Instructions for decontamination/cleaning</p> <p>Instructions for sterilization</p> <p>Any special precautions for handling</p>	<p>N/A</p> <p><i>The device is not cleaned before use. The device is delivered sterile. There is no special handling required.</i></p>	<p><i>Please provide copies of those instructions and validation of the process.</i></p>
<p>11. What records for product release are available:-</p> <p>Indicator testing:-</p> <p>Chemical</p> <p>Biological</p> <p>Dosimetric release</p> <p>Parametric release</p>	See Question 5	<p><i>Please provide information e.g. results and outcome</i></p>
<p>12. Have bioburden determinations been undertaken</p>	See Question 6	<p><i>Please provide information e.g. type (nature), frequency, results, outcome</i></p>
<p>13. Are environmental precautions undertaken on the device during:</p> <p>Manufacturing</p> <p>Sterilization</p>	See Question 7	<p><i>Please provide information e.g. type of controls, frequency of monitoring, results and outcome</i></p>
<p>14. Has a 'standard' been applied to the any of the above processes: International – ISO European – EN British - BSI</p>	YES	<p><i>Please provide the appropriate number and title of the standard</i></p>

		<p><i>Sterilization:</i>  <i>Validation completed to EN 550:</i>  <i>Sterilization of medical devices.</i>  <i>Validation and routine control of ethylene oxide sterilization with reference to: ISO 11135: Sterilization of Healthcare Products by Ethylene Oxide.</i></p> <p><i>Bioburden:</i>  <i>ISO 11737-1:</i>  <i>Sterilization of Medical devices- Microbiological Methods.</i></p> <p><i>Environment</i>  <i>Controls: ISO 14698 and 14644:</i>  <i>Cleanrooms and associated controlled environments</i></p>
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EXCLUSIVELY FOR CLINICAL USE

MR SAFE GUIDE WIRE

Contents

1 MR Safe Guide Wire in protection coil

Instructions For Use

Read the following warnings, precautions and directions for use carefully.

Warnings

Failure to abide by the following warnings might result in damage to the vessel, shearing of the **MR Safe Guide Wire**, and release of plastic fragments from the **MR Safe Guide Wire**. Such pieces or fragments from the wire may have to be removed from the vessel.

- Do not manipulate or withdraw the **MR Safe Guide Wire** through a metal entry needle or a metal dilator. Manipulation and/or withdrawal through a metal entry needle, or a metal dilator may result in destruction and/or separation of the outer polyurethane coating requiring retrieval. A plastic entry needle is recommended when using this wire for initial placement.
- Do not use the **MR Safe Guide Wire** with devices which contain metal parts such as atherectomy catheters or metal introduction devices as they may cause the **MR Safe Guide Wire** plastic coating to shear and/or sever the wire.
- Do not reshape the **MR Safe Guide Wire** by any means. Attempting to reshape the wire may cause damage, resulting in the release of wire fragments into the vessel.
- When exchanging or withdrawing a catheter over the **MR Safe Guide Wire**, secure and maintain the guide wire in place under vision to avoid unexpected guide wire advancement, otherwise damage to the vessel wall by the wire's tip may occur.
- A retrieving device, such as a gripper or basket forceps, can only be used after the **MR Safe Guide Wire** has been removed from the patient's vessel. Using a retrieving device while the **MR Safe Guide Wire** is in the vessel may cause the **MR Safe Guide Wire** to break.
- Manipulate the **MR Safe Guide Wire** slowly and carefully in the vessel while confirming the behaviour and location of the wire's tip under visualisation. Excessive manipulation of the **MR Safe Guide Wire** without fluoroscopic confirmation may result in vessel perforation. If any resistance is felt or if the tip's behaviour and/or location seem improper, stop manipulating the **MR Safe Guide Wire** and/or the catheter and determine the cause by visualization. Failure to exercise proper caution may result in bending, kinking, and separation of the guide wire's tip, damage to the catheter, or damage to the vessel.
- Do not attempt to use the **MR Safe Guide Wire** if it has been bent, kinked or damaged. Use of a damaged wire may result in damage to the vessel or the release of wire fragments into the vessel.

Precautions

- The **MR Safe Guide Wire** should be used by a physician, who is well trained in manipulation and observation of guide wires.
- Sterile in an unopened and undamaged unit package. Do not use if the unit package or the guide wire is broken or soiled. The **MR Safe Guide Wire** should be used immediately after opening the package and be disposed of safely and properly after use, following local regulations for medical waste management.
- When using a drug or a device concurrently with the **MR Safe Guide Wire**, the operator should have a full understanding of the properties/characteristics of the drug or device so as to avoid damage to the **MR Safe Guide Wire**.
- The surface of the **MR Safe Guide Wire** is not lubricous unless it is wet. Before taking it out of its holder and inserting

it through a catheter, fill the holder and the catheter with heparinised physiological saline solution.

- When reinserting the **MR Safe Guide Wire** back into the holder, take care not to damage the wire's hydrophilic coating with the edge of the holder.
- Do not use a metal torque device with the **MR Safe Guide Wire**. Use of a metal torque device may result in damage to the wire. Also, do not slip a tightened up torque device over the wire, as this may result in damage to the wire.
- Due to the slippery nature of the hydrophilic coating and the **MR Safe Guide Wire**, the operator may encounter some difficulties in handling the wire. A non-metal torque device, sold separately, is recommended for easier handling/manipulation of the wire.
- Due to variations of certain catheter tip inner diameters, abrasion of the hydrophilic coating may occur during manipulation. It is advisable to stop using such catheters.
- Do not manipulate the **MR Safe Guide Wire** through a tightened up rotating haemostasis valve, as this may result in damage to the wire.
- After removal from the patient's vessel, and prior to reinserting it into the same patient during the same catheterisation, the **MR Safe Guide Wire** should be rinsed in a bowl full of heparinised physiological saline solution. Any blood residues still adhering to the wire can be removed by wiping once with a gauze pad moistened with heparinised physiological saline solution. Use of alcohol antiseptic solutions or other solvents must be avoided, because they may adversely affect the surface of the **MR Safe Guide Wire**.
- The entire operation should be carried out aseptically.
- The **MR Safe Guide Wire** has been sterilised by ethylene oxide gas. For single use only. Do not resterilise or reuse.
- Avoid exposure to direct sunlight, extreme temperatures and high humidity during storage. Store under controlled room temperature.

Directions For Use

- Remove the **MR Safe Guide Wire** and the holder together from the package.
- Fill the holder with heparinised physiological saline solution through the hub of the holder using a syringe.
- Remove the **MR Safe Guide Wire** from the holder and inspect the **MR Safe Guide Wire** prior to use, to verify if it is lubricated. If the **MR Safe Guide Wire** can not be easily removed from the holder, inject more heparinised physiological saline solution into the holder and try again.
- Prior to use prime the catheter with heparinised physiological saline solution to ensure smooth movement of the **MR Safe Guide Wire** within it.
- The **MR Safe Guide Wire** may slide entirely into the catheter or slip out of the catheter because of its low sliding friction.
- Keep at least 5 cm of the wire extended out of the hub of the catheter during introduction.



Do not use if package is damaged

Contract Medical International GmbH,  
Zur Wetterwarte 50, Haus 302, 01109 Dresden, Germany;  
Tel: +49 351 213 88 88, Fax: +49 351 213 88 99,  
E-mail: [info@contract-medical.com](mailto:info@contract-medical.com), [www.contract-medical.com](http://www.contract-medical.com)



**National Research Ethics Service**  
**King's College Hospital Research Ethics Committee**

Camberwell Building  
King's College Hospital  
94 Denmark Hill  
London  
SE5 9RS

Telephone: 0203 299 3923  
Facsimile: 0203 299 5085

26 June 2009

Professor Reza Razavi  
Professor of Paediatric Cardiovascular Sciences  
Guy's and St Thomas' Hospital  
Rayne Institute,  
St Thomas' Hospital  
Westminster Bridge Rd, London  
SE1 7EH

Dear Professor Razavi

<b>Study Title:</b>	<b>Interventional cardiac catheterisation for congenital heart disease using magnetic resonance imaging</b>
<b>REC reference number:</b>	<b>09/H0808/61</b>
<b>Protocol number:</b>	<b>Version 1.0</b>
<b>EudraCT number:</b>	<b>N/A</b>

The Research Ethics Committee reviewed the above application at the meeting held on 17 June 2009. Thanks to you and Dr Tzifa for attending to discuss the study and confirming the following:

- There have been no patient studies into this technique. 100s of Catheters have been inserted, 40-50 a year, under MRI guidance.
- The procedure is in the last stages of Clinical Trials Authorisation by the MHRA.
- The procedure should take no longer than it would under X-Ray. In pigs it was the same. We will apply an hour and a half cut off in the MRI scanner.
- The diagnostic MRI scan takes 15-20 minutes, the Scan after the procedure takes 15-20 minutes.
- The procedure itself should take no longer than an hour and a half. In difficult cases the fluoroscopic procedure can take up to 3 hours.
- MRI images add clarity of lesions and therefore should be an advantage.
- You will send a copy of the Patient Information Sheet to the GP.
- You will write a Patient Information Sheet for children of 12 years and above.

#### **Ethical opinion**

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

#### **Ethical review of research sites**

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

This Research Ethics Committee is an advisory committee to London Strategic Health Authority  
*The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England*

Research & Development  
Guy's & St Thomas' Foundation NHS Trust  
3rd Floor Conybeare House  
Guy's Hospital  
St Thomas Street  
London SE1 9RT  
Tel: 02071885731

Prof. Reza Razavi  
Professor of Paediatric Cardiovascular Sciences  
Rayne Institute,  
St Thomas' Hospital  
Westminster Bridge Rd, London  
SE1 7EH

07 December 2009

Dear Prof. Razavi,

**Title:** Interventional cardiac catheterisation for congenital heart disease using magnetic resonance imaging

In accordance with the Department of Health's Research Governance Framework for Health and Social Care, all research projects taking place within the Trust must receive a favourable opinion from an ethics committee and approval from the Department of Research and Development (R&D) prior to commencement.

- **Ethics number:** 09/H0808/061
- **Sponsor:** KCL/GSTT
- **Funder:** BRC & British Heart Foundation
- **End date:** 01/07/2010
- **Protocol:** Version 1 01/04/2009
- **Site:** GSTFT
- **R&D approval Date:** 07/12/2009

R&D have reviewed the documentation submitted for this project and I am pleased to inform you that we are approving the work to proceed within Guy's and St Thomas' NHS Foundation Trust and has been allocated the Trust R&D registration number RJ109/N238. Please quote the R&D registration number in any communications with the R&D Department regarding your project.

**Conditions of Approval:**

- The principal investigator must notify R&D of the actual end date of the project.
- The Principal Investigator is responsible for ensuring that Data Protection procedures are observed throughout the course of the project.
- The project must follow the agreed protocol and be conducted in accordance with all Trust Policies and Procedures especially those relating to research and data management.
- R&D must be notified of any changes to the protocol prior to implementation.
- Please submit a copy of the progress report on the anniversary of the Ethics favourable opinion (Anniversary of the Ethics approval 26<sup>th</sup> June)

If appropriate it is recommended that you register with the Current Controlled Trials website;  
<http://isrctn.org/>

Please ensure that you are aware of your responsibilities in relation to The Data Protection Act 1998, NHS Confidentiality Code of Practice, NHS Caldicott Report and Caldicott Guardians, the Human Tissue Act 2004, Good Clinical Practice, the NHS Research Governance Framework for Health and Social Care, Second Edition April 2005 and any further legislation released during the time of this study.

Dear Prof Razavi

## CLINICAL INVESTIGATION: NO OBJECTION

Manufacturer : Contract Medical International GmbH  
Model Name : MR GuideWire  
Model Number : MG-35180-001  
Description : MR Guide Wire  
Your notification dated : 18/09/2009  
Protocol version number : 1  
Number of patients : 20  
Follow-up : as per routine follow-up

I hereby notify you that the UK Competent Authority has no grounds for objection to the making available of the above medical device for the purposes of a clinical investigation as declared in the above notification.

The device(s) must be labeled "*exclusively for clinical investigations*".

The Competent Authority's review of your notification led to some observations which are included at the end of this letter for your consideration. No response is necessary to these observations.

The ethics committee opinion that forms part of the information required under Section 2.2 of Annex VIII must be provided to MHRA as soon as it becomes available. The clinical investigation must not commence at any UK centre until the relevant ethics committee approval is obtained.

MHRA also requires confirmation that each individual site in this clinical investigation has received the necessary approvals. For NHS sites this approval must be obtained from the NHS/HSC R&D office and for non-NHS sites this approval must be obtained from your ethics committee. Please notify MHRA of the outcome of the relevant approvals for each site in this clinical investigation once received. Please note that this clinical investigation must **not** commence in any UK site until you have received the relevant approvals for that individual site and you have notified MHRA of this.

Full details can be obtained from the National Research Ethics Service (NRES) ([www.nres.npsa.nhs.uk](http://www.nres.npsa.nhs.uk)) or by emailing [queries@nationalres.org.uk](mailto:queries@nationalres.org.uk). When contacting NRES you should make it clear that the investigation involves a non-CE marked medical device.

The assessors who assisted with the evaluation of your notification will be sent a copy of this decision, for information only and strictly "in confidence". Our decision will also be notified to the relevant ethics committee(s) if you have confirmed that you are happy for us to do this. If you have not then you may wish to advise them of this decision yourself.

We will retain all the documentation provided by you for one month from the date of this letter. After this time the documentation (except for one copy, retained for record purposes only) will be destroyed, unless you request its return.

### Adverse Incident Reporting

You are reminded that Regulation 16(10)(a) of the Medical Devices Regulations 2002 (SI 618) and Annex X of the Medical Devices Directive 93/42 require you to record fully all adverse incidents and report all serious adverse incidents occurring in the UK to the Competent Authority.

Such reports should be made to the MHRA (devices) Adverse Incident Centre and should include all serious adverse incidents, whether initially considered to be device related or not, that have occurred within the UK.

A "serious adverse incident" is one which:

- led to a death
- led to a serious deterioration in the health of the patient, user or others and includes:
  - a life threatening illness or injury
  - a permanent impairment to a body structure or function
  - a condition requiring hospitalisation or increased length of existing hospitalisation
  - a condition requiring otherwise unnecessary medical or surgical intervention and which might have led to death or serious deterioration in health had suitable action or intervention not taken place. This includes a malfunction of the device such that it has to be monitored more closely or temporarily or permanently taken out of service
- led to foetal distress, foetal death or a congenital abnormality or birth defect
- might have led to any of the above

Such adverse incidents that have occurred in the UK should be reported as soon as possible and in any case within 10 days of occurrence. When reporting these incidents please include the total number of patients treated in the UK at the time of reporting.

Those incidents arising out of the same investigation being carried out at other participating centres, whether European or non-European, should be reported on a three monthly basis in a summary format, since such events may have direct influence on the status of the UK investigation. When providing these summaries please include:

1. The number of serious adverse incidents from all participating centers in a simple tabular format laying out the percentages of each type of serious incident globally and from the UK with an indication as to how many of those are thought to be device related or non-device related.
2. The total number of patients recruited in the UK during that same 3 month period and in total;
3. The total number of patients recruited outside of the UK during that same 3 month period and in total;

In the case of a blinded control clinical investigation using a CE marked device as control, all adverse events should be reported to MHRA in line with the requirements above.

Where an un-blinded controlled clinical investigation is being carried out using a CE marked device as the control, adverse incidents involving the CE marked devices should be reported to the competent authority in line with vigilance guidelines.

All adverse incident reports and manufacturer summary reports should be submitted to the Devices Adverse Incident Centre. We encourage you to use MHRA's manufacturers on-line reporting system (MORE) to submit this information. Details of this simple to use system and how to register for it can be found on the Device Adverse Incident reporting portions of the MHRA website ([www.mhra.gov.uk](http://www.mhra.gov.uk)), along with details of other methods of reporting. If using MORE, please include MHRA's CI reference number in the 'incident description' field.

Please note that adverse events involving a medicinal product should also be reported to MHRA Medicines by the manufacturer of the medicine or sponsor of the study. Information on the requirements for reporting of such events can be found on the MHRA website by clicking on the Yellow Card icon on the right hand side of the home page and then selecting 'Information for the Pharmaceutical Industry' from the left hand menu.

#### **Amendments**

You must notify the Competent Authority of all proposed changes to this investigation and await our letter of no objection before you implement them. This includes changes relating to the device, clinical investigation plan, investigators or investigating institutions, and changes made upon the request of an ethics committee. Failure to notify us of proposed changes could result in the manufacturer being liable to prosecution.

When notifying changes, please provide the following information:

- the reference number shown at the top of this letter.
- the proposed change(s) to the clinical investigation plan/design of device/other study documentation.
- the reason for the change(s).
- a signed statement by or on behalf of the manufacturer that the proposed change(s) do not predictably increase the risk to the patient, user or third party.

#### **Final Report**

Under Regulation 16(10) of the Medical Devices Regulations 2002 (SI 618) the written report of a completed clinical investigation must be kept available for the Secretary of State if required. MHRA may request a copy of the written report for scrutiny.

A letter informing the Competent Authority of when the trial has been completed would be appreciated.

#### **CE Marking**

MHRA would be interested to know when the device under investigation is CE marked and would be most grateful for notification of this once completed.

#### **Competent Authority Comments**

Please ensure that you note and understand the requirements set out above for reporting adverse incidents to the UK Competent Authority.

Yours sincerely

Mr Rob Higgins  
(on behalf of the Competent Authority, UK)

Tel: 020 7084 3185  
Fax: 020 7084 3107  
Email: [Rob.Higgins@mhra.gsi.gov.uk](mailto:Rob.Higgins@mhra.gsi.gov.uk)



## PATIENT INFORMATION SHEET

*We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.*

### **You or your child have been found to have a significant cardiac lesion that requires transcatheter intervention (key hole intervention through major veins and/or arteries of the body).**

#### **What is the purpose of the study?**

Up until now transcatheter cardiac interventions have taken place in the catheterisation laboratory (cath lab) with the aid of fluoroscopy (X-Rays) involving the use of ionising radiation. However, cardiac catheterisations can also be performed under magnetic resonance (MR) guidance, rather than X-Ray imaging. MR guidance provides high resolution and gives an accurate picture of the inside of the heart and heart vessels. Our hospital has pioneered the performance of MR guided diagnostic cardiac catheterisations since 2002, although cardiac interventions have continued to be performed in the traditional catheterisation laboratory. The reason for that has been the unavailability of MR compatible devices, particularly of an MR compatible guidewire, which is essential to guide the cardiac catheters to certain places in or outside the heart and also provide a railtrack for the interventional equipment (balloon catheters and balloon/stent assemblies) to travel on. Such an MR compatible guidewire has now been developed and we are conducting the first clinical trial to assess the feasibility of performing certain transcatheter congenital cardiac interventions solely under MR guidance.

#### **Why have I been chosen?**

You have been chosen because you have been found to have a cardiac problem that requires a transcatheter intervention.

Not all transcatheter interventions are suitable for performance in the MR suite, but your planned procedure is one of those that would be. Your MR-guided intervention will be performed by the same team of Cardiologists that would perform your procedure in the cath lab.

#### **Do I have to take part?**

Taking part in the research is entirely voluntary. It is up to you to decide. We will describe the study and go through this information sheet, which we will then give to you. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

#### **What will happen to me if I take part?**

You or your child will be admitted to hospital as per our cardiac catheterisation protocol.

You will receive no additional pre-catheterisation investigations (such as X-Rays and blood tests) to those we routinely perform prior to cardiac interventions. The recovery period and hospital stay will remain the same. The only difference is that you or your child will have the procedure performed under MR- instead of X-Ray guidance. This might make the catheterisation procedure easier for the operators due to better visualisation of the cardiac structures under MR and will lead to less or no X-Ray radiation being used during the procedure.

the first instance. However, you may not wish to complain to the researcher if he/she is the object of the complaint, and you may wish to make a more formal complaint.

#### **Harm**

In the event that something does go wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against Guy' & St. Thomas' NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

#### **Will my taking part in this study be kept confidential?**

Procedures for handling, processing, storage and destruction of your data are compliant with the Data Protection Act 1998. All information which is collected about you during the course of the research will be kept strictly confidential.

Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it. Your data will be collected from the referral letter and patient notes, as well from your oral information; Data will be electronically stored securely, in an encrypted format; Authorised persons such as researchers, regulatory authorities and Research and Development (for monitoring of the quality of the research) will have access to these data; Data will be retained for 1 year.

#### **Involvement of the General Practitioner/Family doctor (GP)**

Your GP will not be contacted to discuss the trial beforehand but will be notified of the outcome of the interventional procedure.

#### **What will happen to the results of the research study?**

The results of the study will be published in a research paper. You will not be identified in any report/publication.

#### **Who is organising and funding the research?**

The research is organised by Professor Razavi and is partially funded by the Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust.

#### **Who has reviewed the study?**

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity.

This study has been reviewed and given favourable opinion by King's College Hospital Research Ethics Committee.

**A copy of the study information sheet, the interventional catheterisation information leaflet and a signed consent form will be given to you to keep for your records.**

***Thank you for considering taking part and taking time to read this sheet.***



## Children's Information Sheet

### Study Title: Cardiac catheterisation with MRI guidance

Research is a careful process that enables progress in Medicine. This project is to do with performing a key-hole heart intervention without using X-Rays.

**We are asking if you would agree to take part in this project.**

#### **Why have I been asked to take part?**

You have been found to have a heart lesion that requires a key-hole intervention through a big vein and/or artery of your body. We are asking every boy and girl who is scheduled to have such a procedure to come and have it done without the use of X-Rays.

#### **Did anyone check that the study is OK to do?**

Yes. Before any research is allowed to happen it has to be checked by a group of people called an Ethics Committee. They make sure the research is OK to do. Your project has been checked by the King's College Hospital Ethics Committee.

#### **Do I have to take part?**

No. If you do not want to take part then you do not have to.

#### **What will happen to me if I take part in the research?**

You will be admitted to hospital as per our usual routine. You will receive no additional investigations (such as X-Rays or blood tests) to those we routinely perform prior to cardiac interventions. The recovery period and hospital stay will remain the same. The only difference is that you will have the procedure performed under magnetic resonance guidance instead of X-Ray guidance.

#### **Will joining in help me?**

That is the main aim of this research. Performing the procedure with the help of MRI will hopefully make the catheterisation procedure easier for the operators, as we will be able to visualise your heart better, and it will also lead to less or no X-Ray radiation being used during the procedure. Our bodies do not like large and repetitive exposures to X-Rays, but we do have to use them in the hospitals in order to diagnose or treat people when there is no other alternative.

#### **Will my medical details be kept private? Will anyone else know I'm doing this?**

We keep all of your details private. Only people that are allowed will be able to see your scans and your details.



**What if I don't want to do the research anymore?**

If at any time you do not want to the research any more, just tell your parents, doctor or nurse. They will not mind and not be cross with you.

*Thank you for considering taking part and taking time to read this sheet.*

**INFORMATION FOR PARENTS OF CHILDREN UNDERGOING  
DIAGNOSTIC CARDIAC CATHETERISATION**

**Cardiac catheterisation** is performed to obtain information about heart defect/s (or suspected heart defect/s) in order to optimise the child's treatment. This includes no change in the treatment, starting or changing medication, interventional cardiac catheterisation or cardiac surgery. Usually the results are available immediately. In some children, additional tests are needed and in others the final decision will be taken after discussion at the weekly departmental meeting of all the paediatric cardiologists and cardiac surgeons. When it is possible to proceed directly to an interventional catheter at the same time as the diagnostic catheter, then this will have been discussed before the procedure. Rarely, intervention may be considered for the first time at the diagnostic catheter because of unexpected findings. In this situation parental consent will always be obtained before proceeding.

Most cardiac catheterisations are performed under a general anaesthetic, though on occasion a sedative and local anaesthetic is used. The catheters are introduced through the arteries and/or veins in the leg but occasionally in the arm, side of the neck or under the collarbone. A needle puncture is all that is required but rarely a small cut is needed to find the blood vessel. The catheters are used to measure pressures, take blood samples and take X-ray dye pictures at various sites inside the heart. A transoesophageal echocardiogram is sometimes performed at the time of the cardiac catheter by passing a special echo probe down the back of the throat.

**Complications:** All medical procedures, however minor, have associated risks of death or other complications. Cardiac catheterisation in infants and children is no exception to this. Whilst in most patients the risks are very low, it is never possible to guarantee a risk free procedure. **Most complications are minor** but more serious complications can occasionally delay discharge from hospital.

**The risk of death or serious complications is less than 1 in 1000 cases** though it is slightly higher in:

- Newborn or very small children
- Children who are very blue (cyanosed)
- Children with bleeding or clotting disorders
- Children whose heart function is poor
- Interventional catheter procedures
- Radiofrequency ablation procedures

**Complications that can occur in all catheter procedures** include but are not restricted to:

- **Bleeding from the blood vessel** - responds to pressure over the puncture site but if severe may require a blood transfusion.
- **Blood vessel blockage** - a blood thinner (heparin) or clot dissolver (streptokinase) is usually all that is required but rarely surgery is needed to unblock the vessel.
- **Arrhythmias (heartbeat too fast or too slow)** commonly occur while moving the catheters through the heart. Catheter removal is usually all that is needed but rarely medication; an electrical shock or a temporary pacemaker is needed to stabilise the heart rhythm.
- **Blood clot formation** - is usually prevented by the routine administration of blood thinners (heparin) during the catheter. Clots do form rarely but any brain effects are usually transient and a permanent stroke is extremely rare.
- **Catheter perforation of the heart and valve damage** are rare. Usually no action is required but needle aspiration of blood from around the heart is sometimes performed and rarely a surgical repair is required.
- **Anaesthetic complications** include drowsiness, vomiting, chest infection and temperature.

These notes are not meant to be comprehensive and parents should feel free to ask any questions they may have about cardiac catheterisation in their child.

*Please attach a copy to the consent form and give a copy to the parents.*

More serious risks include:

- heart rhythm disturbances
- injury to the heart
- rarely allergic reaction to the dye used to take pictures of the heart.
- The most serious risk is that your child could have a stroke or die as a result of the catheterisation.

These are extremely rare events, but you must discuss the procedure in detail with the cardiologist who will be performing this. You will be required to give consent.

#### Common questions asked about heart catheterisation

##### *Will my child be fully asleep for the cardiac catheterisation?*

Interventional catheterisations require the child to be absolutely still, so your child will be given a general anaesthetic by the anaesthetist and will be asleep. Once asleep, a breathing tube will be inserted and the child's breathing will be assisted by the breathing machine (ventilator). Please ask the anaesthetist any related questions prior to the catheterisation.

##### *Will my child be in pain during the catheterisation?*

No. Children who are fully asleep do not feel pain from the catheterisation. After the catheterisation, the child may feel soreness around the area of the groin puncture site and this can be relieved by giving paracetamol. This will be given by the nursing/medical staff.

##### *Can I watch the catheterisation procedure?*

No. It is not possible for family to watch as care, similar to an operating theatre, is taken to prevent infection, so only doctors, nurses and technicians are in the room with the child.

##### *Can I go with my child to the catheterisation theatre?*

Yes. You can accompany the child to the theatre and stay on till the child is anaesthetised. You will be informed by the nursing staff, so that you can return when your child has recovered from the catheterisation and has woken up in the recovery room.

##### *How long will the catheterisation take?*

Each case varies, but generally the catheterisation takes several hours. The child may be away from the ward for 2-4 hours.

##### *When will I know the results of the catheterisation?*

The cardiologist, who performed the catheterisation, will tell you all the information that is available soon afterwards. The final recommendations about the need for further catheterisation or surgery will not be made until all the cardiologists and heart surgeons have reviewed all the results. This may be 1-2 weeks later. Ask your child's doctor about when you can expect to hear the final results.

##### *Will the x-rays harm my child?*

All x-rays are potentially harmful. The risk is unknown at present but is thought to be minimal. The smallest amount possible is used.

##### *Can the device move from its intended position?*

When stents or closure devices are used, there may be movement of these into a wrong position. This is uncommon and is usually detected at the time of placing the device, when attempts will be made to correct it immediately. Rarely the device can move after the end of the catheterisation, which is why an x-ray and echocardiogram are performed later that day or the next day.

##### *Will my child need to go to intensive care unit after the catheterisation?*

Usually no. If the catheterisation is prolonged or complex, then your child may need to be nursed in the intensive care unit for a few hours.

##### *Will my child need a blood transfusion?*

Not usually. Blood loss during the catheterisation is small and does not need to be replaced. Ask if the doctor expects an unusual amount of blood loss. Rarely, there may be sufficient blood loss from the groin site to require a blood transfusion.

##### *Will my child need new medicines after the catheterisation?*

Sometimes aspirin or a blood thinner is used after an interventional catheterisation. Your child's doctor will let you know what medications need to be given. If a blood thinner, such as warfarin, is used, sometimes your child will need to stay in the hospital for a few days until the medicine has had a chance to work. The ward will provide you with the appropriate medicines on discharge.

If you have any questions not answered here or if you require further information, please ask the staff.

This information sheet does not replace informed consent for the actual catheterisation.

Department of Congenital Heart Disease,  
Evelina Children's Hospital, Guy's & St Thomas' NHS Trust



Study Number: Ref 09/H0808/61

Patient Identification Number for this trial:

## CONSENT FORM

Title of Project: Cardiac catheterisation with MRI guidance

Name of Researcher: Prof. Reza Razavi / Dr Shak Qureshi

Please initial box

1. I confirm that I have read and understand the information sheet dated 25/11/2008 (version 1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

☐

3. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

☐

4. I agree to take part in the above study.

☐

\_\_\_\_\_  
Name of Patient

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Name of Person taking consent  
(if different from researcher)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Researcher

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical notes